IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GbR, Plaintiff, v. ELI LILLY AND COMPANY, and BROOKSHIRE BROTHERS, INC., Defendants.	)	CASE No. 2:15-cv-01202-WCB

PLAINTIFF UROPEP'S COMBINED OPPOSITION TO DEFENDANTS' MOTIONS FOR SUMMARY JUDGMENT

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Plaintiff ERFINDERGEMEINSCHAFT UROPEP GbR ("UroPep") submits this opposition to two motions for summary judgment by Defendants Eli Lilly and Company and Brookshire Brothers, Inc. (collectively "Lilly").[1] UroPep will refer to Lilly's Motion for Summary Judgment of Non-Infringement and its supporting memorandum as "Lilly 112 ¶ 6 Br." and to Lilly's Motion for Summary Judgment of Invalidity and its supporting memorandum as "Lilly WD Br." UroPep respectfully requests an oral hearing concerning Lilly's motions.

COUNTER STATEMENT OF THE ISSUES

1. Is "an inhibitor of phosphodiesterase (PDE) V" as used in claim 1 of the '124 patent a means plus function limitation?

2. If "an inhibitor of phosphodiesterase (PDE) V" is construed as "a compound able to inhibit phosphodiesterase (PDE) V" could a reasonable juror conclude that Lilly has failed to meet its burden of presenting clear and convincing evidence that the asserted claims are invalid for failure to satisfy the written description requirement?

3. If "an inhibitor of phosphodiesterase (PDE) V" is a means plus function limitation as used in claim 1 of the '124 patent, is tadalafil within the scope of the claim?

[1] By agreement of the parties, and with the Court's approval (Dkt. No. 128), UroPep is opposing both of Lilly's motions in a single responsive brief. UroPep will also file a single sur-reply.

SUMMARY OF THE ARGUMENT

As of July 1997, the class of agents known as PDE5 inhibitors was well-described and the field of PDE5 inhibitor discovery was mature. Pfizer was just months away from launching its PDE5 inhibitor sildenafil (Viagra), which would go on to become one of the most successful drugs in history. At the same time, the published literature already contained hundreds of PDE5 inhibitors, in part because no less than six pharmaceutical companies, including Pfizer and ICOS (later the Lilly ICOS joint venture) had long-running and well-publicized research programs.

UroPep was not one of those companies. The '124 patent inventors did not purport to come up with even a single new PDE5 inhibitor, much less invent the hundreds of compounds that had already been discovered by others. Instead, the UroPep inventors saw what none of these major pharmaceutical companies did — that PDE5 was present and played a functional role in the human prostate, and PDE5 inhibitors could therefore be used to treat benign prostatic hyperplasia ("BPH"). Both of Lilly's motions are predicated on a false premise — that UroPep tried to get a patent on a novel set of pharmacologic agents instead of inventing a new medical treatment for a specific disease using an already well-known class, PDE5 inhibitors.[2]

The invention is a medical treatment method and, "[f]or a method claim, § 112, paragraph 6 is implicated only when steps plus function without acts are present." *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1028 (Fed. Cir. 2002). Lilly has not argued that claim 1 of the '124 patent contains any step plus function limitation (nor could it), and its entire means plus function argument never gets past *Epcon Gas* and the subsequent cases applying its rule.[3] Moreover, Lilly has

[2] *See, e.g.*, Lilly WD Br. 9 ¶ 26 (misstating that UroPep asserts that tadalafil infringes the asserted claims of the '124 patent, as opposed to the use of tadalafil to treat BPH).

[3] Though UroPep has consistently argued that 112 ¶ 6 does not apply to the "inhibitor of phosphodiesterase (PDE) V," it regrets that it did not bring *Epcon Gas* to the Court's attention earlier. This line of authority establishes that method claims should not be construed to include

collapsed the search for a generic structural placeholder into its quest to find a purely functional modifier to that placeholder. These two distinct requirements of means plus function applicability cannot be found in the same word and yet Lilly insists they are both "inhibitor." Lilly's motion for summary judgment of non-infringement requires this Court to ignore clear rules from the Federal Circuit and therefore must be denied.

As for written description, the law that pertains to method and composition claims is the same, but in the course of pharmaceutical and medical innovation, the facts can be very different. Lilly repeats over and over again the erroneous assertion that development of PDE5 inhibitors as of July 1997 was in its early days. Lilly wants to pretend as if the state of play in this case is the same as it was in *University Of Rochester v. G.D. Searle & Company*, 358 F.3d 916 (Fed. Cir. 2004), where the patentee tried to claim a method of COX-2 enzyme inhibition when zero COX-2 enzyme inhibitors were known to the patentee or published in the prior art. But in July 1997, hundreds of PDE5 inhibitors were known, including Lilly's tadalafil, and the field of developing and discovering PDE5 inhibitors was anything but nascent. This is a fact issue of central importance to Lilly's motion, and on which it has misstated the state of the science.

Lilly's surgery on the words of the inventors of sildenafil, Drs. Nicholas Terrett and Andrew Bell, paints a false picture for the Court. In 1996, Drs. Terrett and Bell stated "*Prior to our work*, very little had been reported on the design, synthesis and screening of selective cGMP PDE inhibitors." Lilly Ex. 12, Terrett 1996, App. at 0318 (emphasis added). By Lilly's own expert's admission, the person of skill in the art would know that the Pfizer work of Drs. Terrett and Bell began prior to

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means plus function limitations. And even without reference to *Epcon Gas*, a means plus function interpretation is wrong for the reasons given in UroPep's earlier briefing as well as those discussed here.

1990. Ex. 50,[4] Deposition of David Rotella ("Rotella Dep.") at 88:12-20, App. at 0956 (admitting that he himself reviewed a Pfizer sildenafil patent application published in 1992 in the relevant time frame); 89:11-17, App. at 0957 (agreeing a person of skill in the art would have been aware of this patent application in the mid-1990s); 90:12-18, App. at 0957 (agreeing that a person of skill in the art would have known, based on this application, that Pfizer's work on PDE5 inhibitors began before June 1990). Yet, through selective quotation of this sentence without the "Prior to our work" italicized above, Lilly presented to the Court a mistaken assertion regarding the state of development of PDE5 inhibitors.[5] *See* Lilly WD Br. at 3; Ex. 4, Rotella WD Decl. ¶¶ 32, 8.b (using same words without attribution), App. at 0097, 0105-06. Dr. Bell, one of the co-inventors of sildenafil and UroPep's expert, explains as much. Ex. 78, Declaration of Andrew Bell in Support of UroPep's Opposition to Defendants' Motions for Summary Judgment ("Bell Decl.") ¶¶ 19-31, App. at 1571-73.[6]

The first Pfizer patent application published in 1991, with a priority date of 1990, *id.* ¶ 22, Ex. 51, CA 2044748A1 (published 12/21/1991, bearing priority date of 6/20/1990), App. 0988. Lilly's own expert Dr. Rotella remembers reviewing the January 2, 1992 European publication of this application in the "mid-1990s" when he was working in the field as a person of skill. Ex. 50,

[4] For convenience of the Court, UroPep begins its exhibit numbers with 50, as Lilly ended its with 49. The parties have agreed that UroPep will include additional exhibits in sequential numbering and prepare a Joint Appendix that contains all of the exhibits sequentially.

[5] To shore up its "uncertain and unpredictable" argument, Lilly pairs its misstatement of the Terrett 1996 article with the fact that as of July 1997 the role of PDE5 and its distribution in the human body were poorly understood. *See* Lilly WD Br. at 3 n. 7; Ex. 4, Rotella WD Decl. ¶32, App. at 0106 (citing Lilly Exs. 13, 14; "Coste 1995" and "Beavo 1995"). This latter point is true, and it is why the UroPep inventors made a true discovery.

[6] UroPep expert Dr. Terrett unfortunately could not continue in this case because he has taken a senior research position with Merck and Co. and his new employer will not permit him to act as an expert witness.

Rotella Dep. 88:12 - 90:18, App. at 0956-57; Ex. 52, EP 463756A1, App. at 1038. Thus no one of reasonable skill in the art could credibly assert that the Pfizer work in fact began in 1996, nearly on the eve of the launch of the fruits of that work (sildenafil) and with a clinical program ongoing. Ex. 78, Bell Decl. ¶¶ 28-29, App. 1573. That is why Lilly and its expert have to resort to eliminating part of the quote from Terrett 1996 to distort the state of the art in 1996 and, by extension, 1997. At the least, the state of the art in July 1997 is a disputed fact issue that precludes summary judgment, particularly so when taking into consideration Lilly's burden of proof.

Yes, the UroPep inventors needed to disclose a representative number of PDE5 inhibitors to demonstrate possession of their inventive therapy. And for a new use of a known class of compounds that representative number is not large. Because this analysis takes place against the backdrop of the prior art and the knowledge of a person of skill, not by holding against the inventors the failure to recopy that which is well known into their patent application. The Federal Circuit has said time and time again that the required extent of disclosure depends on "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (internal quotation omitted).

Lilly gets the law wrong and ignores the knowledge of a person of skill — holding it against UroPep that the field of PDE5 inhibitors was occupied by a variety of structures in July of 1997. Lilly's expert admitted over and over again that he based his invalidity opinion on the '124 patent specification's silence as to structural motifs of PDE5 inhibitors well known in the art in July 1997:

> Q. The linear tetracyclic scaffold that you're referring to of tadalafil, was disclosed to persons of skill in the art in the 1995 PCT application we earlier discussed, correct?
>
> A. That's correct.
>
> ***

> Q. The failure of the '124 patent inventors to include the linear tetracyclic structure type of tadalafil in the '124 patent contributed to your conclusion that the claims of the '124 patent lack written description, correct?
>
> A. Along with many other examples as I've indicated.

Ex. 50, Rotella Dep. at 48:18-22, 63:11-16, App. at 0946, 0950. Dr. Rotella is not himself to blame, he got the wrong instructions on the law from Lilly. *Id.* at 65:20-66:3, App. at 0951.

When the law that applies to all inventions is applied to the facts of this one, a fact-finder could reasonably conclude that UroPep disclosed far more than was required under the rule articulated in *Ariad*. Because the '124 patent is directed to an audience that Lilly admits was aware of hundreds of PDE5 inhibitors, including tadalafil, the UroPep inventors did not need to copy this voluminous and known work of others into their patent application. They demonstrated possession of their new treatment using this known class by disclosing the example PDE5 inhibitors in their application, which would be read against the backdrop of the knowledge of a person of skill. In this environment, the '124 patent disclosure is more than sufficient.

LEGAL STANDARD

"Summary judgment is granted 'if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.'" *Raytheon Co. v. Indigo Sys. Corp.*, 688 F.3d 1311, 1314-15 (Fed. Cir. 2012) (quoting Fed. R. Civ. P. 56(a)). When reviewing a summary judgment ruling, the court "'views all evidence in the light most favorable to the non-moving party and draws all reasonable inferences in that party's favor.'" *Id.* at 1315 (quoting *Griffin v. United Parcel Serv., Inc.*, 661 F.3d 216, 221 (5th Cir. 2011)) (applying Fifth Circuit law and reversing grant of summary judgment where the dispute presented fact issues). "Viewing the evidence in the light most favorable to" the nonmoving party, "a genuine issue of material fact [] precludes summary

judgment." *Optical Disc Corp. v. Del Mar Avionics*, 208 F.3d 1324, 1339 (Fed. Cir. 2000) (reversing grant of summary judgment).

"Whether certain claim language invokes 35 U.S.C. § 112, ¶ 6 is an exercise in claim construction and is therefore a question of law." *Personalized Media Commc'ns, LLC v. Int'l Trade Com'n*, 161 F.3d 696, 702 (Fed. Cir. 1998). Claim elements that do not use the word "means" create a rebuttable presumption that § 112 ¶ 6 does not apply. *See Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1348-49 (Fed. Cir. 2015) (en banc) ("[T]he presumption can be overcome and § 112, para. 6 will apply if the challenger demonstrates that the claim term fails to recite sufficiently definite structure or else recites function without reciting sufficient structure for performing that function.") *Id.* at 1349 (citations and quotations omitted).

"Infringement, whether literal or under the doctrine of equivalents, is a question of fact." *Absolute Software, Inc. v. Stealth Signal, Inc.*, 659 F.3d 1121, 1129-30 (Fed. Cir. 2011). "Whether an accused device or method infringes a claim with a § 112, ¶ 6 limitation, i.e., whether it performs the identical function with the same structure, materials, or acts described in the specification or an equivalent thereof, is a question of fact." *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1430 (Fed. Cir. 2000). In a motion for summary judgment of noninfringement, "[t]he moving party bears the burden of demonstrating the absence of genuine issues of material fact." *Conroy v. Reebok Int'l., Ltd.*, 14 F.3d 1570, 1575 (Fed. Cir. 1994) (partially reversing grant of summary judgment of noninfringement).

"Compliance with the written description requirement is a question of fact, and summary judgment is proper if and only if no reasonable fact finder could return a verdict for the non-moving party on the issue." *Scriptpro, LLC v. Innovation Assocs., Inc.*, 762 F.3d 1355, 1359 (Fed. Cir. 2014) (citation and quotations omitted). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had

possession of the claimed subject matter as of the filing date." *Ariad Pharm.*, 598 F.3d at 1351. "[D]etermining whether a patent complies with the written description requirement will necessarily vary depending on the context. . . . For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.'" *Id.* (quoting *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005)).

ARGUMENT

I. THE CLAIM TERM "AN INHIBITOR OF PHOSPHODIESTERASE (PDE) V" IS NOT A MEANS PLUS FUNCTION TERM UNDER § 112 ¶ 6

Method claims generally cannot have means plus function claim terms. The only way method claims invoke § 112 ¶ 6 is if they contain step plus function terms.[7] Lilly's argument to the contrary runs afoul of *Epcon Gas*, where the Federal Circuit stated unequivocally that "[f]or a method claim, § 112, paragraph 6 is implicated only when steps plus function without acts are present." 279 F.3d at 1028. And invocation of means plus function requires both a nonce word (a generic placeholder for a structure that provides no specific structure, like "means" or "module") and then purely functional modifier language. Manual of Patent Examining Procedure ("MPEP") § 2181. Yet Lilly tries to assign nonce status to "inhibitor" and then call the same word a functional modification of itself. The claim does not say "means for inhibition of PDE5."

Even putting aside these authorities, the claim term at issue here is structural, not functional, as it discloses a compound capable of inhibiting PDE5. UroPep has extensively briefed this issue and the Court needs no reminder of the presumption that without the term "means" the claim does

[7] Lilly has never asserted that the claims of the '124 have step plus function terms. And, as explained below, such a contention is foreclosed by applicable case law.

not invoke § 112 ¶ 6, or that the skilled person would understand "inhibitor" in the context of the '124 patent to be a compound capable of inhibiting PDE5.

Lilly has cited no cases and UroPep is unaware of any in which a court has construed "inhibitor" as a means plus function limitation in a method of treatment. In addition, it is worth pointing out that the word "inhibitor" has been construed in other enzyme inhibition cases consistent with UroPep's proposed construction here. And it is further worth looking at the numerous patents, including those of Lilly, whose claim scope and validity would be drawn into question were this Court to conclude that "inhibitor" is a purely functional claim term in the chemical arts.

The Court should construe "an inhibitor of phosphodiesterase (PDE) V" as "a compound able to inhibit phosphodiesterase (PDE) V," because method claims cannot have means plus function limitations and because, even if they could, this claim term is not purely functional.

A. Method Claims Generally Cannot Have Means Plus Function Limitations

"For a method claim, § 112, paragraph 6 is implicated only when steps plus function without acts are present." *Epcon Gas*, 279 F.3d at 1028 (citing *O.I. Corp. v. Tekmar Co., Inc.*, 115 F.3d 1576, 1583 (Fed. Cir. 1997) ("structure and material go with means, acts go with steps"). Claims 1 and 3 of the '124 patent recite methods of treatment, and therefore should not be construed to contain means plus function limitations.

This case is similar to *Alza Corp. v. Mylan Laboratories, Inc.*, 349 F. Supp. 2d 1002 (N.D. W.Va. 2004).[8] In *Alza* the method claims required that a "therapeutic dose" of the active ingredient be administered orally. *Id.* at 1011. The generic defendant argued that "therapeutic dose" was a means

[8] The reasoning of Chief Judge Keeley in this case was adopted *en toto* by Chief Judge Walker of the Northern District of California in a subsequent case involving the same patent. *Alza Corp. v. Impax Labs., Inc.*, No. C-03-4032 VRW, 2005 WL 6220093, at *2 (N.D. Cal. Mar. 10, 2005).

plus function limitation claiming the function of getting the dose into the patient — and that therefore the claim was limited to the structure of the osmotic pump system disclosed in the specification. *Id.* The *Alza* court concluded that "[t]he *Epcon Gas* and *O.I. Corp.* decisions unquestionably dictate the construction of method claims in conjunction with § 112, ¶ 6" and that therefore the subject method claims could not contain a means plus function limitation. *Id.* at 1012. The court also concluded that because the claim recited an act, "administering," that it could not be a step plus function claim. *Id.* So too, here, the asserted claims of the '124 patent are methods, barring a means plus function interpretation. And they recite the act of "administering," barring a step plus function interpretation.

While this Court is bound by *Epcon Gas*,[9] Lilly's position that "an inhibitor of phosphodiesterase (PDE) V" is purely functional is also transparently incorrect in that it uses the same term for the required generic structural placeholder and the required functional modifier to that generic placeholder — an impossible contradiction.

[9] Since *Epcon Gas*, the Federal Circuit has once permitted a means plus function construction of a method claim, without citing *Epcon Gas* and with the parties apparently not disputing applicability of means plus function interpretations to method claims. *On Demand Mach. Corp. v. Ingram Indus., Inc.*, 442 F.3d 1331, 1340 (Fed. Cir. 2006). The district courts (other than the *Alza* courts) have sometimes passed on this question without citing *Epcon Gas* and concluded that *On Demand* is an outlier occasioned by the patentee's use of "means" language in the method claim at issue. *See, e.g.*, *Semcon Tech, LLC v. Micron Tech., Inc.*, No. CV 12-532-RGA, 2014 WL 4447017, at *6 (D. Del. Sept. 9, 2014) (finding no applicability of means plus function to method claim and distinguishing *On Demand* because patentee there had used "means" in the claim). To the extent *On Demand* needs to be reconciled with *Epcon Gas*, it stands for the proposition that when the patentee explicitly invokes "means" in a method claim, then a means plus function interpretation may be possible despite *Epcon Gas*'s bar. That is not the case here and so the Court need not resolve any perceived conflict.

B. Lilly Must Identify A Nonce Word And A Purely Functional Limitation — The Same Word In The Claims Cannot Be Both

The MPEP sets out the examination requirement for applicability of § 112 ¶ 6, and states that a means plus function claim that does not contain the word "means" must instead use a "generic placeholder" (nonce word), that is then "modified by functional language."

> Accordingly, examiners will apply 35 U.S.C. 112(f) or pre-AIA 35 U.S.C. 112, sixth paragraph to a claim limitation if it meets the following 3-prong analysis:
> (A) the claim limitation uses the term "means" or "step" or a term used as a substitute for "means" that is a generic placeholder (also called a nonce term or a non-structural term having no specific structural meaning) for performing the claimed function;
> (B) the term "means" or "step" or the generic placeholder *is modified by functional language*, typically, but not always linked by the transition word "for" (e.g., "means for") or another linking word or phrase, such as " "configured to" or "so that"; and
> (C) the term "means" or "step" or the generic placeholder is not modified by sufficient structure, material, or acts for performing the claimed function.

MPEP § 2181 (emphasis added); *Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1351 (Fed. Cir. 2015) ("module" was generic placeholder and function was "for receiving communications transmitted between the presenter and the audience member computer systems and for relaying the communications to an intended receiving computer system and for coordinating the operation of the streaming data module"). The same word in a claim cannot be both the generic placeholder and supply the functional modification. To say it is the former is to say it is intended to be a generic substitute for structure. To say it is the latter is to say it is not intended to be structure at all.

Even beyond *Epcon Gas* and assigning impermissible double duty to the word "inhibitor," Lilly's argument fails. Lilly's position conflicts with how the word "inhibitor" has been construed by other courts, and Lilly calls into question the claim scope and validity of potentially thousands of patents, including many of Lilly's own.

C. No Other Court Has Ever Construed "Inhibitor" As A Purely Functional Term

This Court is not the first to be asked to construe a claim term containing the word "inhibitor" in a patent relating to enzyme inhibition. In *Avanir Pharm., Inc. v. Actavis S. Atl. LLC*, No. CA 11-704-LPS, 2012 WL 6019095, at *3 (D. Del. Dec. 3, 2012), the asserted claims included the term "a debrisoquin hydroxylase inhibitor." The claims did not require any specific inhibitor and recited no additional structure for the claimed inhibitors. *Id.* Yet no one, not the parties and not the Court, suggested that "a debrisoquin hydroxylase inhibitor" was a means plus function term, even when it was used in an apparatus claim. *Id.* The *Avanir* court construed this term as "[a] compound capable of inhibiting the oxidation of dextromethorphan by the liver enzyme debrisoquin hydroxylase, excluding cimetidine" [which had been disclaimed in prosecution, rather like the exclusion of certain compounds from the claims of the '124 patent]. *Id.* at *4.[10]

Lilly has not identified a single decision that construed a claim term reciting "inhibitor" as subject to § 112 ¶ 6. As in *Avanir*, other courts in pharmaceutical patent cases have routinely construed this term in accordance with UroPep's proposal. *See, e.g.*, *Schering Corp. v. Mylan Pharm., Inc.*, No. CIV.A. 09-6383 JLL, 2011 WL 2446563, at *15 (D.N.J. June 15, 2011) (construing "HMG CoA reductase inhibitor" in an independent claim containing no additional structural limitations as "a substance that, when provided externally, results in the inhibition of 3-hydroxy-3methylguraryl coenzyme A reductase."). Putting Lilly's position in perspective shows how radical and wrong it is even if *Epcon Gas* had not foreclosed the applicability of means plus function to methods. That perspective includes, potentially, thousands of patents and dozens of Lilly's.

[10] We will return to the patent at issue in *Avanir* in the context of Lilly's written description argument — because this patent, which was litigated through to judgment against one of the most sophisticated generic defendants, is certainly invalid under Lilly's "structural diversity" theory. This and hundreds of other new pharmaceutical methods relying on known agents are threatened by Lilly's opportunistic position in this case.

D. The Implications Of Holding That § 112 ¶ 6 Applies Are Pervasive And Potentially Devastating To Existing Patents, Including Lilly's

There are 27,465 United States patents with claims that use the word "inhibitor."[11] While, of course, not all of them will address the same pharmaceutical context as this case, even casual review of them shows numerous patents that could be dramatically impacted by Lilly's argument. For example, U.S. Patent No. 9,393,238 issued July 19, 2016 and is assigned to Celgene. Ex. 53, App. at 1065. It claims a method of treating non-Hodgkins lymphoma with a specific compound combined with a second active substance. In claim 1, the second active substance is just claimed as an "anticancer agent," which if Lilly were judging the hypothetical infringement case would presumably also receive § 112 ¶ 6 treatment (again putting aside *Epcon Gas*). App. at 1094. And claim 9 says the second active agent could be a "proteasome inhibitor." *Id.* The specification discloses no specific examples of proteasome inhibitors. Therefore Lilly's position that "inhibitor" is subject to § 112 ¶ 6 would render this claim invalid for indefiniteness because there was a "failure" to provide corresponding structure. That is just one example. Lilly's position here is extreme and its own patents prove it.

Lilly owns 34 patents that claim the use of an "inhibitor" without reciting any additional structure for that inhibitor in the patent claim.[12] As just one example, Lilly's U.S. Patent No. 5,674,887 claims a "method of treating or preventing the excessive resoption of bone comprising the administration of an effective amount of a pharmaceutically acceptable inhibitor of xanthine oxidase

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[11] http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=0&f=S&l=50&TERM1=inhibitor&FIELD1=ACLM&co1=AND&TERM2=&FIELD2=&d=PTXT (last visited August 7, 2016). The Court can take judicial notice of government records like those held at the USPTO and searchable on its website. *See Paleteria La Michoacana, Inc. v. Productos Lacteos Tocumbo S.A. DE C.V.*, No. CV 11-01623 (RC), 2016 WL 3034150, at *16 n.13 (D.D.C. May 27, 2016) (taking judicial notice of information publicly available on USPTO website).

[12] See Ex. 54, App. at 1096, Summary Chart Of Lilly Patents With Claim Term "Inhibitor."

sensitive to bone disorders to a patient in need of said treatment." Ex. 55 at col. 11, ll. 25-29, App. at 1109. No structural limitations beyond "inhibitor" are present, and yet Lilly's view is that it was acceptable to claim all xanthine oxidase inhibitors. Ex. 55 at col. 4, ll. 22-26, App. at 1105 ("It will be understood by the pharmaceutical chemist to whom this document is addressed that xanthine oxidase inhibitors are numerous, and that the present invention may be carried out with any of the class of pharmaceutically acceptable xanthine oxidase inhibitors."). And yet now, Lilly maintains UroPep's analogous claims are subject to the limitations of the claims § 112 ¶ 6 and, if not, invalid for lack of written description. Patent law does not countenance one rule for Lilly's patents and another for UroPep's.

Closer to this case would be Lilly's use of the claim term "selective PDE5 inhibitor" and, more generically, "PDE5 inhibitor" in its own issued U.S. patents. United States Patent No. 6,451,807 is directed to uses of a "selective PDE5 inhibitor" to treat sexual dysfunction in specific patient subpopulations. Ex. 56 at col. 20, ll. 45-56, App. at 1121. Presumably Lilly would have § 112 ¶ 6 apply to this claim as well. Of course, *Epcon Gas* and common sense precludes such an application. Yet, in 1999 Lilly filed this patent application, claimed the use of all selective PDE5 inhibitors, and told the world:

> Selective PDE5 inhibitors vary significantly in chemical structure, and the use of a selective PDE5 inhibitor as defined in the present invention is not dependent on a particular chemical structure, but rather on the critical parameters outlined herein.

Id. col. 7, ll. 3-7, App. at 1115. Lilly did not identify all the then-known types of selective PDE5 inhibitors. Ex. 78, Bell Decl. ¶ 66, App. at. 1590. But Lilly received valuable patent rights utterly at odds with its opportunistic desire to deprive UroPep of its invention through mistaken invocation of § 112 ¶¶ 1 and 6. And this was not the only time Lilly thought it was all right to prosecute a patent invoking the entire class of "PDE5 inhibitors," *see infra* 38-40. The Court should not permit Lilly to

acquire patent rights under one regime and advocate for another when accused of infringement of the patent rights of others.

II. THE CLAIMS OF THE '124 PATENT ARE NOT INVALID FOR FAILING TO SATISFY THE WRITTEN DESCRIPTION REQUIREMENT

Lilly's written description motion cites a total of seven cases, never identifies the standard the Court should apply to its motion, gets the law wrong in several places, and makes no effort to draw from the cases any kind of guiding principle that would aid the Court.

While Lilly tells the Court that written description is "based upon the specification and not what the applicants for the patent may (or may not) have known," Lilly WD Br. 11, it leaves out that the analysis must incorporate the knowledge of a person of ordinary skill. *See, e.g.*, *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before.") (internal citation omitted). Because it ignores this aspect of the law, Lilly repeatedly attempts to rest its case on how special tadalafil's tetracyclic structure is. Lilly WD Br. 14-15. But special or not, this is irrelevant because Lilly all the while admits that the tetracyclic structure (not to mention tadalafil's status as a PDE5 inhibitor) was known to a person of ordinary skill in the art in 1997. *See* Ex. 50, Rotella Dep. at 48:18-22, App. at 0946; Ex. 4, Rotella WD Decl. ¶ 64, App. at 0119; Ex. 78, Bell Decl. ¶ 46, App. at 1582; *see also* Lilly 112 ¶ 6 Br. at 9, ¶ 21. The UroPep inventors do not need to demonstrate that they specially possessed what was already known to the whole world — tadalafil and hundreds of other PDE5 inhibitors. They needed to demonstrate only that they possessed the invention that PDE5 inhibitors would treat BPH. Lilly does not even challenge the only proposition that matters.

Lilly's invocation of *Rochester* and *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014) is off point. In each of these cases the development in the subject field was truly nascent — indeed they can be described as "time zero" cases because in each there were *zero* embodiments either of the entire subject genus (*Rochester*), or of anything like the accused product (*AbbVie*) known in the art. On the other side of the development timeline are authorities Lilly never discusses, like *Application of Herschler*, 591 F.2d 693 (C.C.P.A. 1979), which are far more analogous to this case. The Federal Circuit described the important points of *Herschler* and distinguished the case in *Rochester*.

> In *Herschler*, the court found adequate written description support for broad claims to processes for topically administering a physiologically active steroidal agent to a human or animal by concurrently administering the steroidal agent and dimethyl sulfoxide ("DMSO"), even though the specification disclosed only one example of a "physiologically active steroidal agent." Critically, however, there was no question in that case that, unlike "non-steroidal compound[s] that selectively inhibit[ ] activity of the PGHS–2 gene product," numerous physiologically active steroidal agents were known to those of ordinary skill in the art. As the court there noted, "[w]ere this application drawn to novel 'steroidal agents,' a different question would be posed." 591 F.2d at 701. The novelty in that invention was the DMSO solvent, not the steroids.

Rochester, 358 F.3d at 928. The novelty in this case is the method of treatment, not the PDE5 inhibitors.

Once the Court considers the true state of the art on PDE5 inhibitors in July 1997, shorn of Lilly's mistaken reading of the Terrett 1996 article, *see supra* 4-5, and taking into account the fact that tadalafil and hundreds of other PDE5 inhibitors were known, the differences between this case and *AbbVie* or *Rochester* become apparent. It is not enough for Lilly to incant abstract statements of the law because, because, as the en banc court observed in *Ariad*, "[w]hatever inconsistencies may appear to some to exist in the application of the law, those inconsistencies rest not with the legal standard but with the different facts and arguments presented to the courts." 598 F.3d at 1352.

Lilly has committed the obverse sin here, pointing to factually dissimilar cases like *Rochester* and *AbbVie* and declaring that the legal conclusions from those cases necessarily apply here. Lilly is left accusing UroPep of having claims that cover lethal doses of "natural products" as treatments for BPH or of failing to describe later-invented PDE5 inhibiting *antibodies* that are either not covered by the claim, or whose description was unnecessary precisely because they are later-invented.

The broader ramifications of Lilly's rule that "structurally diverse" classes, even if well-known for their structural diversity, can never be the subject of a new therapeutic invention, are extreme. Lilly's position here is belied by its own statements in patents it obtained for PDE5 inhibitors and also other "structurally diverse," but well-known, classes of compounds, such as non-steroidal anti-inflammatory drugs (NSAIDs), or kinase inhibitors. In July 1997, the class of PDE5 inhibitors was well-known and suitable for a ground-breaking therapeutic invention applicable to the class, whatever the chemical "structural diversity" might have been.

To the extent Lilly doubles down on its misstatement of the state of the art there is at least a fact issue for the jury. But the truth is the skilled person would have been aware of hundreds of PDE5 inhibitors, including Lilly's tadalafil, and the UroPep inventors demonstrated possession of their method by illustrating several example PDE5 inhibitors. They needed to do no more. The Court should deny Lilly's summary judgment motion.

A. *Rochester* And *AbbVie* (As Well As Other Cases) Demonstrate The Consequences Of Prosecuting Genus Claims When The State Of The Art Is Truly Nascent Or The Accused Product Truly Unknown And Different — Not When Hundreds Of Members Of The Subject Class, Including The Accused Product, Are Indisputably Known

Lilly's reliance on *Rochester* and *AbbVie* is misplaced, because these cases are factually removed and involve, respectively, development "time zero" when little to nothing is known about the subject genus (*Rochester*), and an attempt to cover a competitor's unknown and wildly different

product with examples of only a very different species of the genus (*AbbVie*). In this case, with hundreds of PDE5 inhibitors well-known, including Lilly's tadalafil, a different result obtains.

In *Rochester*, a hypothesis that the COX-2 enzyme was responsible for certain inflammatory processes led the university to develop a screening assay to determine whether a drug would inhibit COX-2 without also inhibiting COX-1. *Rochester*, 358 F.3d at 918. The idea was that COX-1 inhibition caused the undesirable side effects of then-existing NSAIDs. *Id.* The university obtained a patent on "[a] method for selectively inhibiting [COX-2] activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the [COX-2 enzyme] in a human host in need of such treatment." *Id.*; *see also id.* n. 1.

The Federal Circuit held the patent invalid for failing to satisfy the written description requirement because:

> [I]t is undisputed that the '850 patent does not disclose any compounds that can be used in its claimed methods. The claimed methods thus cannot be practiced based on the patent's specification, even considering the knowledge of one skilled in the art. No compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known.

Id. at 927; *accord Ariad*, 589 F.3d at 1353 (describing this holding of *Rochester*). *Rochester* drew distinction with *Herschler*, where all physiologically active steroids were claimed even though only one was described in the specification, because "there was no question in that case that, unlike 'non-steroidal compound[s] that selectively inhibit[ ] activity of the [COX-2 enzyme],' numerous physiologically active steroidal agents were known to those of ordinary skill in the art." 358 F.3d at 928. As *Herschler* had noted, it's not as if the patentee there had tried to claim "novel steroidal agents." *Id.* (citing *Herschler*, 591 F.3d at 701).

So, when numerous members of the claimed class are known (*Herschler*) a method of using them can be patented even though the specification mentions only one of them because they are

expected to share the same property that makes them suitable for the invention. Whereas when there are zero examples of a class in the specification and zero known to the skilled person, a method of using that class of compounds will be invalid for lack of written description. Into which category does this case fit? The facts point to only one conclusion. The UroPep inventors did not purport to claim "novel PDE5 inhibitors" and wrote their patent when numerous PDE5 inhibitors were known.

AbbVie confirms the critical role of the state of knowledge regarding the claimed genus and the difference (in application of the law to the facts, not the legal test, *Rochester*, 358 F.3d at 926) between claims for a novel class of compounds and claims for a new use of already-known compounds. In *AbbVie*, the desire for and benefits of antibodies that performed a function (neutralize IL-12 with low K_{off}) were well known, but it was not known how to make such antibodies. The patents purported to solve this, and disclosed examples of antibodies that were all derived from one group (Joe-9), and had similar type chains (VH3 type heavy and Lambda type light). The claims, however, encompassed any fully human antibodies that neutralized IL-12. Janssen's accused Stelara antibody was derived from an entirely different antibody class than those disclosed in AbbVie's patents and had different heavy and light chain types. Because of the misalignment between the scope of the disclosure and scope of the claims, the Federal Circuit upheld the jury's verdict of no written description.[13] *Id.* at 1302. In this case, the scope of the

[13] Lilly also neglects to mention the procedural posture of *AbbVie*, which is the analytical opposite of this summary judgment motion. In *AbbVie*, the Federal Circuit was reviewing the denial of a JMOL motion after a jury had already found the subject patent invalid for lack of written description. Thus the question was whether any reasonable fact-finder could have so found, viewing all facts in the light most favorable to the verdict. 759 F.3d at 1297. Here the facts must be viewed in the light most favorable to UroPep, the non-movant. Lilly further is silent on the fact that the district court in *AbbVie* denied summary judgment of no written description, holding that "the state of the art is a factual issue disputed by the parties" and that "[t]his factual dispute regarding the state of the art alone precludes summary judgment." *Abbott GMBH & Co., KG v. Centocor Ortho Biotech, Inc.*, 870 F. Supp. 2d 206, 238 (D. Mass. 2012).

disclosure (PDE5 inhibitors are useful in treating BPH, and why) aligns perfectly with the scope of the claims (treatment of BPH with PDE5 inhibitors).

Lilly over-reads *AbbVie* because, of course, if Stelara (or something like it) had been known to a person of skill in the art, AbbVie's failure to describe such antibodies, like Herschler's failure to describe more than one "physiologically active steroid," would have been excusable. There is no suggestion in *AbbVie* that the Stelara-type antibodies were known (indeed how could AbbVie have a patent that covered a previously-known antibody invented by someone else?).[14] *Rochester* and *LizardTech* (and numerous other cases) make clear that the patentee need not describe that which is already known. Here, the problem solved by the UroPep inventors is not how to identify or create PDE5 inhibitors, as tadalafil (and approximately 100 compounds structurally similar to it, Ex. 78, Bell Decl. ¶ 46, App. at 1582) was indisputably known to a person of skill in the art in July 1997, Ex. 4, Rotella WD Decl. ¶ 64, App. 0119. Because the problem UroPep solved and the invention it claimed is the novel treatment of BPH using a known class of compounds, tadalafil's purported uniqueness is not remotely similar to the unknown *and* undescribed Stelara antibody of *AbbVie*.

Nor are Lilly's other authorities any more helpful to it. *In re Alonso*, 545 F.3d 1015, 1021 (Fed. Cir. 2008) is effectively the same case as *Rochester* with the only difference being that the patentee had attempted to claim all of a brand new subject class of antibodies having only disclosed one (as opposed to the zero that the university disclosed in *Rochester*). *Alonso*, 545 F.3d at 1021. Again, Alonso was not trying to patent a specific new therapy using a well-known class of compounds — he was trying to patent the use of an entirely new and underexplored class of

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[14] This again underscores the factual difference between composition and method inventions. If Stelara had been known when AbbVie filed its genus claim for all IL-12 antibodies, then AbbVie's genus composition claim would have been unpatentable as anticipated. AbbVie did not invent a new use of a known class of antibodies. It invented some antibodies and tried to claim all antibodies that could do what AbbVie's could. UroPep invented a therapy using a well-known class of PDE5 inhibitors — a class that included the well-known PDE5 inhibitor tadalafil.

compounds by disclosing only one. Into the same bucket goes *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1126 (Fed. Cir. 2008),[15] where the Federal Circuit found a lack of written description for a claim to all bacterial *polA* genes because of the embryonic state of the art, holding "the record here shows that only three bacterial *polA* genes out of thousands of genes had been cloned." *Id.*

Rounding out the principal cases in this area is another where written description was found lacking because the specification admitted that the art was in its early days. In *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353 (Fed. Cir. 2011), the patentee claimed "drug-eluting stents utilizing 'rapamycin, or a macrocyclic lactone analog thereof' as the therapeutic agent." *Id.* at 1358. The specifications only disclosed rapamycin and nowhere disclosed any analog. *Id.* at 1364. Though the art disclosed two such analogs, the court stated that "[a]ny suggestion that these references represented existing knowledge in the art so well known as to excuse including a more detailed disclosure of the macrocyclic lactone analogs genus in the specification is belied by the state of the art at the time of the invention." *Id.* at 1364. Crucially, the specifications admitted that the art was in its infancy and that the mechanism of rapamycin was "still under active investigation." *Id.* at 1365.

The written description requirement for a claim invoking a genus element can be satisfied, all agree, by "disclosure of … a representative number of species falling within the scope of the genus …." *Ariad*, 598 F.3d at 1350. What the cases demonstrate is that sometimes, when the genus of compounds is well known (*Herschler*) the representative number is one; whereas at other times, when the art is in its infancy or the accused product differs substantially from what was known (*Boston*

[15] Lilly mistakenly references *Carnegie Mellon* and states that this case also involves "biological subject matter." Lilly WD Br. 12. The '124 patent claim term at issue "an inhibitor of phosphodiesterase (PDE) V" does not involve biological subject matter. The examples disclosed, and all known PDE5 inhibitors in July 1997 are not produced using recombinant means, are not gene-encoded, and do not involve amino acid or DNA sequencing.

Scientific or *AbbVie*) one or even several described species will not be enough. There is no "bright-line rule[] governing, for example, the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention, and it changes with progress in a field." *Ariad*, 598 F.3d at 1351. Lilly relies on cases in which the field and the patents were nothing like the state of the art in this case — *Rochester* and *AbbVie* — while failing to cite a single case where a new therapeutic use for a well-known class of compounds was found invalid for lack of written description. There is no such case, and there can be no doubt that the diverse world of PDE5 inhibitors, including Lilly's tadalafil, was well known in July 1997.

B. The Diverse World Of PDE5 Inhibitors, Including Lilly's Tadalafil, Was Well Known In July 1997

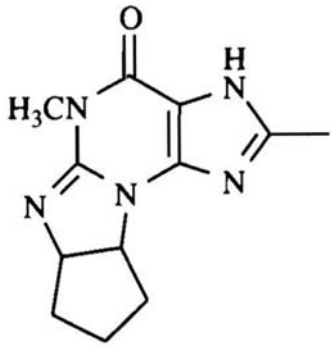
The UroPep inventors did not purport to, and did not, contribute novel PDE5 inhibitors to what was already a dense and mature area of research. In July 1997, literally hundreds of PDE5 inhibitors were known in the art, including approximately one hundred structurally similar to tadalafil as disclosed in Lilly's published patent application, along with tadalafil itself. The whole world was aware of the "structural diversity" that Lilly now thinks is dispositive. Lilly's motion rests on its factually mistaken assertion that, in July 1997, "very little had been reported on the design, synthesis and screening of selective cGMP PDE inhibitors," Lilly WD Br. 3 (truncating in quotation and simultaneously misinterpreting Terrett 1996, Ex. 12, App. at 0318); *see* Ex. 78, Bell Decl ¶¶ 19-31, App. at 1571-73. In fact, much had been reported on these subjects by July 1997, even though little had been done *prior to the work* of UroPep's experts Drs. Terrett and Bell, the fathers of Viagra. Their work began in 1985, and, inspired by them, the rest of the world had taken up the baton.

1. Sybertz 1995

By 1995, several pharmaceutical companies had published, in patents or the peer-reviewed literature, numerous PDE5 inhibitors that had significant structural diversity. E.J. Sybertz, et al.,

cGMP Phosphodiesterase Inhibition: A New Mechanism for the Discovery of Therapeutic Agents, Current Pharm. Design 1995, 1, 373-390, Ex. 57, App. at 1124-41 (cited in Ex. 6, Terrett Decl. ¶ 23, App. 181), methodically discusses these PDE5 inhibitors. *See* Ex. 78, Bell Decl. ¶ 38, App. at 1576-80. Lilly's expert recalled reading this article in "1997 or 1998" when he was working in the field. Ex. 50, Rotella Dep. at 45:12-18; 46:16-18, App. at 0946.

First mentioned are the guanine derived PDE5 inhibitors by Schering-Plough, of which Sybertz shows eight. Ex. 57 at Table I, App. at 1125; Ex. 50, Rotella Dep. 46:19-47:6, App. at 0946. These are drawn from Schering-Plough's U.S. Patent 5,393,755, which discloses seventeen PDE5 inhibitors. Ex. 58, App. at 1143-74; Ex. 78, Bell Decl. ¶ 41, App. at 1581.



The compound at the left is Schering-Plough's selective PDE5 inhibitor, shown as compound 1d in the Sybertz review article. The Court has probably already observed that this compound is tetracyclic,[16] Ex. 78, Bell Decl. ¶ 39, App. at 1580-81, just like (as we are repeatedly informed in Lilly's brief) tadalafil is tetracyclic. *See, e.g.*, Lilly WD Br. 9, 15, 18. This is the first of many times that Lilly's insistence that there is some significance to the '124 patent's omission of tadalafil or other tetracyclic structures can be discarded.[17] *Id.* at 18 (ascribing significance to the fact that "the '124 Patent not only fails to describe any species that is representative of tadalafil, but also

[16] Also disclosed here in Table I is the spiro-tetracyclic compound **Ig**, which structurally similar to the compound Dr. Rotella cites and agrees was also known in 1997, Ex. 4, Rotella WD Decl. ¶ 65, App. at 0119 (citing Ex. 28, Xia 1997, App. at 0464).

[17] The same goes for Lilly's expert's observation that *tri*cyclic PDE5 inhibitors were known in the art in July 1997. Ex. 4, Rotella WD ¶ 63, App. at 0118 ("a person of ordinary skill in the art would know that PDE5 inhibitors may have core structures of more than one or two fused rings"). If the skilled person knows these things there is no need for the '124 patent inventors to repeat them. Again, the invention is a treatment, not a PDE5 inhibitor or class of PDE5 inhibitors.

fails to describe myriad other species of PDE5 inhibitors that were known in the art in 1997"). Lilly is ignoring *Rochester*, *LizardTech* and the numerous authorities establishing that the knowledge of a person of skill is brought to the table. That would include knowledge of Schering-Plough's patent, and the Sybertz review article.

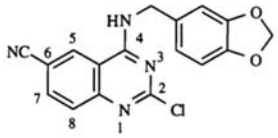
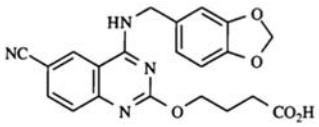
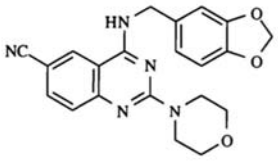
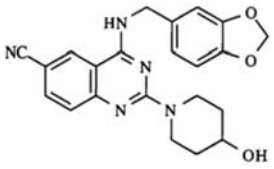
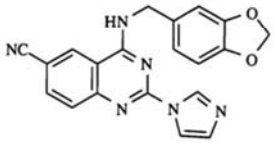
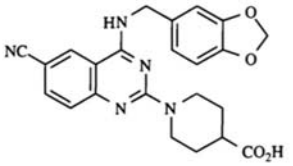
Following the erroneous instructions he received from Lilly's counsel, Lilly's expert admitted that he held it against the '124 patent that these known tetracyclic structures are not in the '124 patent specification.

> Q. In your view, the failure of the '124 patent inventors to disclose the sharing plow [sic] structure type in the '124 patent contributes to their failure to have disclosed a representative number of compounds for the genus of PDE5 inhibitors, correct?
>
> MR. VARE: Objection; form.
>
> A. That is a contributing factor, yes.

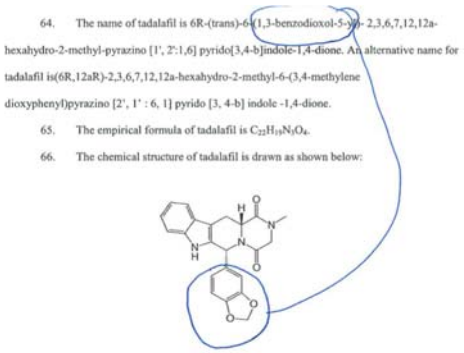
Ex. 50, Rotella Dep. 59:1-8, App. at 0949.

Second up in this review article are the numerous PDE5 inhibitors developed by Eisai. Sybertz shows twenty-two Eisai PDE5 inhibitors. Ex. 57 at Tables IV and V, App. at 1127-29; Ex. 50, Rotella Dep. 49:17-50:2, App. at 0947; Ex. 78, Bell Decl. ¶ 38, App. at 1576-80. These include the following structures from Table V:

Table V. Structures and Activity of Potent Eisai PDE Type V Inhibitors

	Structure	IC_{50} (nM) Type V
Va		32
Vb		2
Vc		5
Vd		6
Ve		0.8
Vf		2.6

Ex. 57, App. at 1129, Table V. Notably, all of these Eisai structures share something in common with tadalafil, the 3,4-methylenedioxyphenyl (sometimes called 1,3-benzodioxol-5-yl, *see* Ex. 50, Rotella Dep. at 41:11-22, App. at 0945) moiety (the bicyclic part of the molecules with the two oxygens shown in the upper right of each). Ex. 50, Rotella Dep. 50:3-6, App. at 0947.[18] Lilly's expert circled this moiety in his deposition. Ex. 50, Rotella Dep. 41:11-22, App. at 0945; Rotella Dep. Ex. 2 (at left), App. at 0985. This same structure is in the '124 patent example PDE5 inhibitors (d) and (f). Ex. 78, Bell Decl. ¶ 61, App. at 1588-89; Ex. 1, '124 patent col. 3, App. at 004. It turns out this structure is significant for how tadalafil (and the Eisai compounds shown in the '124 patent and above) bind to PDE5. Ex. 78, Bell Decl. ¶ 62,


64. The name of tadalafil is 6R-(trans)-6-(1,3-benzodioxol-5-yl)- 2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione. An alternative name for tadalafil is(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene dioxyphenyl)pyrazino [2', 1' : 6, 1] pyrido [3, 4-b] indole -1,4-dione.

65. The empirical formula of tadalafil is $C_{22}H_{19}N_3O_4$.

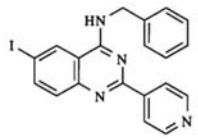
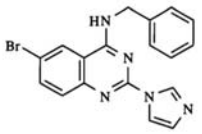
66. The chemical structure of tadalafil is drawn as shown below:

[18] The Eisai group had first published on its series of compounds in 1993. *See* Ex. 26, Takase 1993, App. at 0450. In this article the compounds listed in the '124 patent as examples (c), (f) and (j) are disclosed and data is provided for them. *Id.* at 3766, App. at 0451 (MY5445 is example (c), compound FL-55712 is example (j), and compound 6 is example (f) of the '124 patent); Ex. 1, '124 patent at cols. 3, 4, App. at 004; Ex. 78, Bell Decl. ¶ 36, App. at 1575.

App. at 1589. Lilly does not address this important structural similarity between tadalafil and the '124 patent examples.

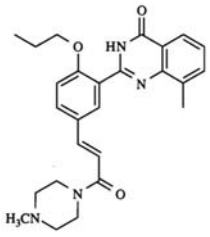
The third group of compounds in Sybertz are those from Ono, of which Sybertz provides examples of two. Ex. 57 at Table VI (shown right), App. at 1130; Ex. 50, Rotella Dep. at 51:1-6, App. at 0947; Ex. 78, Bell Decl. ¶ 38, App. at 1576-80. These are drawn from an Ono patent application, EP 579 496, Ex. 59, App. at 1176, which discloses several additional PDE5 inhibitors. *Id.* at 18, Table I, App. 1193; Ex. 78, Bell Decl. ¶ 43, App. at 1581.

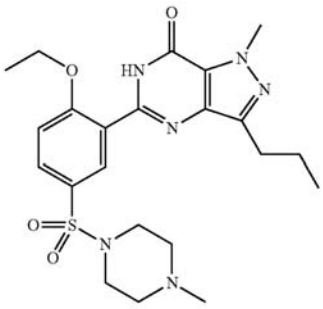
Table VI. Structures and Activity of Ono PDE Type V Inhibitors

	Structure	IC_{50} (nM) Type V
VIa		4.2
VIb		2.8

Sybertz next reports on the work of Drs. Bell and Terrett from Pfizer, showing five of their highly selective and potent PDE5 inhibitors. Ex. 50, Rotella Dep. at 54:7-15, App. at 0948; Ex. 78, Bell Decl. ¶ 38, App. at 1576-80. Lilly's expert opined that these Pfizer compounds represent several different structural types, not represented by sildenafil (which is in the '124 patent). Ex. 57, Table VII (below), App. at 1130; Ex. 1, '124 patent col. 3 (on right showing sildenafil), App. at 0004; Ex. 50, Rotella Dep. at 62:5-8, App. at 0950. He then made clear that he was also holding the failure to include these structural types in the '124 patent against UroPep. *Id.* at 62:9-63:16, App. at 0950. Sybertz cited these from Pfizer's patent applications, just the first of which discloses fifty-eight compounds that have PDE5 inhibitory activity. Ex. 78, Bell Decl. ¶ 44, App. at 1581. Pfizer patent applications provide even more example PDE5 inhibitors, all published

Table VII. Structures and Activity of Pfizer Selective PDE Type V Inhibitors

	Structure	IC50 (nM) Type V	IC50 (nM) Type III
VIIa		6.5	>100000

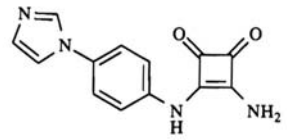
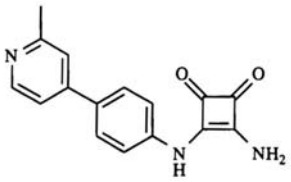


well before July 1997. *See* Ex. 60, WO 93/07149 at 32, App. at 1296; Ex. 78, Bell Decl. ¶ 44, App. at 1581; Ex. 61, WO 94/00453 at 18, App. at 1331; Ex. 78, Bell Decl. ¶ 44, App. at 1581.

Sterling-Winthrop's PDE5 inhibitors reside in Table VIII of Sybertz and there are eight. Ex. 50, Rotella Dep. at 57:7-9, App. at 0949; Ex. 57, Table VIII, App. at 1131; Ex. 78, Bell Decl. ¶ 38, App. at 1576-80. These include WIN58237, which is also shown in the '124 patent as example (i). Ex. 1, '124 patent col. 4, App. at 0004.

In Table IX are two SmithKline Beecham PDE5 inhibitors with a structure type dissimilar from the examples in the '124 patent. Ex. 50, Rotella Dep. at 64:18-22, App. at 0950; Ex. 57; Table IX, App. at 1132; Ex. 78, Bell Decl. ¶ 38, App. at 1576-80. Leaving absolutely no doubt that he was misinstructed on the law, Dr. Rotella summarized his opinion that the non-disclosure of these well-known structure types in the '124 patent helped him arrive at his conclusion of invalidity.

Table IX. Structures and Activity of SmithKline Beecham Cyclobutenedione PDE Type V Inhibitors

	Structure	IC_{50} (nM) Type V
IXa		6000 - 110000[a]
IXb		6000 - 110000[a]

> Q. Turning to Table 9, this was the first round of SmithKline Beecham PDE Type 5 inhibitors, and earlier you volunteered that this structure type is not in the '124 patent, correct?
>
> A. That's correct.
>
> Q. And along with other structure types that were well known in July of 1997, the failure of the '124 patent inventors to disclose this structure type contributes to your opinion that the '124 patent claims are invalid for lack of written description, correct?
>
> MR. VARE: Objection; form.
>
> A. That is a factor that contributed to it.

Ex. 50, Rotella Dep. at 64:18-65:5, App. at 0950. The same exchange occurs as to seven more PDE5 inhibitors from SmithKline Beecham in Table X.

> Q. And I've asked this question several times, but I'll ask it specific to Table 10. The failure of the '124 patent inventors to disclose the structure type that is in Table 10 of the Sybertz 1995 review article, along with other structure types, contributed to your opinion that the '124 patent claims lack written description, correct?
>
> A. Based on information provided to me by counsel, yes.

Id. at 65:20-66:3, App. at 0950; Ex. 57, Table X, App. at 1132; Ex. 78, Bell Decl. ¶ 38, App. at 1576-80.

In total, the Sybertz article gives data and shows 54 PDE5 inhibitors, with a diversity of structural motifs including tetracyclic compounds. In 1995, with the publication of this review article and the sources from which it draws, the person of skill in the art would already be aware of approximately one-hundred PDE5 inhibitors. Ex. 78, Bell Decl. ¶¶ 39, 45, App. at 1580-82. But of course Lilly's own contribution to the knowledge of a person of ordinary skill in the art has not yet been discussed.

2. WO 95/19978 — Lilly's tadalafil patent

On July 27, 1995 WO 95/19978 was published. Ex. 8, WO 95/19978, App. at 0198. It gives over one-hundred examples of tetracyclic PDE5 inhibitors, including tadalafil in Example 95. Ex. 8 at 32-71, App. at 0231-0270; Ex. 78, Bell Decl. ¶ 46, App. at 1582. Lilly's expert admits that tadalafil was known in 1997, based on this patent publication. Ex. 50, Rotella Dep. at 30:6-11, 35:1-18, App. at 0942-43; Ex. 3, Rotella 112 ¶ 6 Decl. ¶ 63, App. at 0058. He further admitted that the other one-hundred and eighteen PDE5 inhibitors in this publication were known. Ex. 50, Rotella Dep. 44:16-21, App at 0945.

In July 1997, based on just these references along with the prior work cited within them, hundreds of PDE5 inhibitors of a diverse range of chemical structures were known to the person of

skill in the art. Ex. 78, Bell Decl. ¶ 45, App. at 1582. These include tetracyclic chemical structures (from Schering-Plough and Lilly's own tadalafil patent application) as well as numerous others, displaying the very chemical structure diversity that Lilly relies on so heavily. But it is precisely because so many of these PDE5 inhibitors were known, and their chemical structural diversity so widely published and discussed, that the inventors of the '124 patent did not need to recite them all in order the claim a method of using PDE5 inhibitors to treat BPH and adequately demonstrate possession of their invention.

C. Given The Advanced State Of The Art, The '124 Patent Inventors Recited More Than Enough Representative Compounds To Demonstrate Possession Of Their Therapeutic Invention

As the foregoing shows, in July 1997 the field of PDE5 inhibitors was not in its infancy, nor was it true that "very little had been reported on the design, synthesis and screening of selective cGMP PDE inhibitors," Lilly WD Br. 3 (truncating quotation and simultaneously misinterpreting Terrett 1996, Ex. 12, App. at 0318); *see supra* 4-5; Ex. 78, Bell Decl ¶¶ 19-31, App. at 1571-73. When the art is advanced, nothing in logic or law requires an inventor to copy hundreds of known compounds into his patent application on a new therapy using a known class of agents. The '124 patent inventors provide ten example compounds and the skilled person would be aware of hundreds more. Moreover, the '124 patent provides the scientific explanation for the invention. Ex. 1, '124 patent col. 2, ll. 6-16; col. 7, ll. 14-34, App. at 0003, 0006. The discovery that PDE5 inhibitors would be useful for treating BPH is the invention, not the list of exemplar PDE5 inhibitors.

In this circumstance the listed examples in the '124 patent are like the one "physiologically active steroid" example provided in *Herschler*. This case is also like *Application of Fuetterer*, 319 F.2d 259, 260 (C.C.P.A. 1963), a case whose reasoning is endorsed in *Herschler*. *Herschler*, 591 F.2d at 701

("[w]e wish to maintain the line first clearly drawn in *In re Fuetterer*").[19] In *Fuetterer*, the claim was to a "rubber stock for producing tire treads" and required "an inorganic salt that is capable of holding a mixture of said carbohydrate and protein in colloidal suspension in water . . . ." 319 F.2d at 260-61. The court first rejected the notion that the inorganic salt term was improper functional claiming. *Id.* at 263. But, more importantly for this case, the court went on and, in a passage quoted in full in *Herschler*, stated:

> Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

319 F.2d at 265 (quoted in *Herschler*, 591 F.2d at 701). By now that should sound familiar, because it is this case.

Calling the UroPep invention a "research proposal" for finding PDE5 inhibitors, Lilly WD Br. 20, misses the point that the UroPep inventors possessed a real therapeutic invention usable the day they filed for their patent with already-known compounds, both disclosed in the '124 patent and known to the person of skill.[20] *Rochester*, by contrast, involved a true research proposal — no COX-2 inhibitors were discovered by the inventors or known in the art.

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[19] *Herschler*'s adoption of *Fuetterer*'s reasoning is important because at least one Federal Circuit panel has observed that *Fuetterer* is not binding, as it represents the opinion of only two judges on a five-judge panel. *See Boston Scientific*, 647 F.3d at 1362 n.4 (Fed. Cir. 2011). While that is accurate, strictly speaking, the binding *Herschler* opinion endorses the reasoning of *Fuetterer*, so it makes no difference.

[20] Also off-point (in more than one way) are Lilly's remarks on the file history of the parent patent to the '124. Citing irrelevant documents concerning a restriction requirement, Lilly WD Br. 19 (citing

All Lilly has left is to accuse UroPep of having invented a therapy that can use too many PDE5 inhibitors. According to Lilly, UroPep's claims are invalid because natural products could be used, and because UroPep failed to describe far-future embodiments, including the use of an antibody to PDE5 publicly disclosed in 2013 and classes of PDE5 inhibitors that may not even exist (irreversible inhibitors). Neither point has purchase.

D. The '124 Patent Need Not Describe Later-Developed Embodiments, And Covers Natural Products Only If They Can Be Given In An "Effective Amount" To Treat BPH Though PDE5 Inhibition

Lilly expresses concern that the '124 patent invention and UroPep's construction of "an inhibitor of phosphodiesterase (PDE) V" leaves it possible to infringe UroPep's claims using an antibody to PDE5 published in 2013 and natural products that have been around for "centuries." *See* Lilly WD Br. 9 ¶ 27 (describing icariin, an ingredient in Horny Goat Weed), ¶29 (referring to unspecified PDE5 inhibitors not known in July 1997 but citing Ex. 4, Rotella WD Decl. ¶ 55 *et seq*), App. at 0114 (containing, at ¶ 74, a reference to such an antibody, earlier referenced in ¶ 51 (citing Ex. 24, Alsheyab 2013, App. at 0435)).

Ex. 49 at App. 0836-37; 0854-58), Lilly says they are a written description rejection over a claim covering "quinazolines and "pyrazolopyrimidones." Not so.

For completeness, the examiner in the prosecution of the '061 patent did issue such a written description rejection, but based it on the misunderstanding that the '124 patent discloses no examples of these two genera. Ex. 62, '061 Patent File History at 5, App. at 1347 ("in the instant application no specific species of quinazolines and their trimethoxy derivatives and pyrazolopyrimidones are disclosed."). There can be no dispute that this was a misunderstanding, as Lilly's own expert has admitted that the '124 patent has examples of compounds in these classes. Ex. 3, Rotella 112 ¶ 6 Decl. ¶ 37, App. at 0049 (admitting compounds (d) and (f) from the '124 patent are quinazolines); *see also* Ex. 1, '124 patent col. 3, App. at 0004, compounds (d) and (f) (the latter of which is a "trimethoxy quinazoline")); Ex. 3, Rotella 112 ¶ 6 Decl. ¶ 40, App. at 0050 (admitting that compounds (g) and (i) from the '124 patent are pyrazolopyrimidones).

Lilly's final observation that if a narrower claim lacks written description a broader claim must also lack written description, Lilly WD Br. 19, is an elementary mistake of patent law. No one doubts that if the '124 patent inventors attempted to claim the specific use of avanafil (a compound not even known in the art in 1997, but possible to have been added by amendment during prosecution) that narrower claim would lack written description.

As to the antibody, Lilly's argument (which does not even make it into its opening brief except through a series of cross-citations) fails on two fronts.[21] First, a skilled person reading the specification would conclude that "an inhibitor of phosphodiesterase (PDE) V" did not include antibodies to PDE5 that would not be discovered for over a decade after the priority date. All of the example PDE5 inhibitors, and indeed all of the hundreds of known PDE5 inhibitors as of the priority date, were small molecules. Ex. 6, Terrett Decl. ¶¶ 22-24, App. at 0181-82; Ex. 78, Bell Decl. ¶ 58, App. at 1587. Second, even if the use of this PDE5 antibody is encompassed by the UroPep claims, that is perfectly fine because "[t]he law does not require the impossible. Hence, it does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention." *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985). As Judge Patel put it,

> Imagine that the Wright Brothers had patented a method for flying, comprising a wing with certain physical characteristics. Assume the wing material was claimed generically and the patent provided one working example of an airplane with wooden wings. Later-developed airplanes used titanium wings. Because the Wright Brothers had not described titanium wings in their application, and had admitted in depositions that it would have been undue experimentation at the time to do so (either because titanium did not exist or was not used in that manner at the time of filing the patent application), their claimed flying method was held invalid for lack of written description.
>
> This outcome contravenes the patent laws.

Regents of Univ. of California v. Dako N. Am., Inc., No. C 05-03955 MHP, 2009 WL 1083446, at *10 (N.D. Cal. Apr. 22, 2009).

And for Horny Goat Weed, luteolin, red grape extracts, gingko biloba, and caffeine, the natural products Lilly mentions, Ex. 4, Rotella WD Decl. ¶ 50, App. at 0112, whether they can be

[21] So too with the alleged coverage of "irreversible" PDE5 inhibitors. Lilly's expert admitted he was not aware of any such inhibitors even today. Ex. 50, Rotella Dep. 68:7-68:8, App. 0951-52.

used in the claimed invention of UroPep depends on whether they can be given in an "effective amount" to treat BPH through PDE5 inhibition. Dr. Rotella conceded he had not bothered to calculate what amounts of these natural substances would be needed to replicate the effectiveness of 5mg of tadalafil (the dose for BPH in Cialis). Ex. 50, Rotella Dep. at 14:9-16:19, App. at 0938.

As Lilly points out, Horny Goat Weed contains what we now know is a PDE5 inhibitor, icariin. Lilly WD Br. 9. Lilly and its expert do not mention that icariin is present in Horny Goat Weed in less than one percent by weight. Ex. 78, Bell Decl. ¶¶ 75-76, App. at 1592-93. Coupled with icariin's potency relative to tadalafil's, and knowing tadalafil's dose for BPH, one can calculate how much Horny Goat Weed a person would have to eat to practice UroPep's claims. Ex. 78, Bell Decl. ¶ 76, App. at 1593. And if anyone has ever eaten over a pound of Horny Goat Weed in a day there might be some benefit for BPH. But this is really an argument about the obviousness of the UroPep claims (and it is not obvious to eat large quantities of Horny Goat Weed, and there is no evidence that anyone has treated BPH by administering such quantities), and has nothing to do with whether UroPep described its invention of using PDE5 inhibitors to treat BPH.[22]

Worse is Lilly and its expert's mention of caffeine, without any citation of the literature on caffeine and PDE5. Ex. 50, Rotella Dep. at 17:6-24, App. at 0939. Caffeine is a very weak PDE5 inhibitor with a potency about one million times lower than sildenafil. Ex. 78, Bell Decl. ¶ 78, App. at 1594; Ex. 16, App. at 0368, J. Corbin and S. Francis, *Molecular Biology and Pharmacology of PDE-5-*

[22] The same issue obtains with luteolin, gingko biloba, and these other plants that Lilly is talking about. For example, lutolin is present in sage in an extremely low weight percentage. Ex. 63, App. at 1351, S. Karakaya and S. EL, *Quercetin, luteolin, apigenin and kempferol contents of some foods. Id.* at Table 1, App. at 1353, Luteolin's IC_{50} against PDE5 allows the same calculation that Lilly's expert did not do. It leads to the conclusion that a person would have to eat thousands of kilograms of sage in a day in order to receive the same level of PDE5 inhibition as 5mg of tadalafil. Ex. 78, Bell Decl. ¶ 77, App at 1593. This is the essence of the "tomato juice" issue — if someone has to drink 50 gallons of juice in a day to get an effective amount of whatever PDE5 inhibitor that juice contains, the '124 patent inventors can hardly be faulted for failing to describe such lethal (and therefore inoperative) "embodiments" of their invention.

Inhibitor Therapy for Erectile Dysfunction, J. Andrology, 24, S38-S41 (2003). As sildenafil and tadalafil have similar potencies, this means that the daily dose of caffeine to effectively treat BPH is much higher than a 5mg dose of tadalafil in Cialis. Ex. 78, Bell Decl. ¶ 78, App. at 1594. In fact, the approximate necessary dosage of caffeine is in the kilograms. *Id.* But the *lethal* dose of caffeine in a human is approximately 5 *grams*. *Id.* These natural products are a total distraction. And suggesting that one could treat BPH by going to Starbucks, as Lilly did at the *Markman* hearing, is the apotheosis of this irrelevant discussion. Ex. 64, App. at 1359, Excerpted Transcript of Claim Construction Hearing at 81:16-19, *UroPep v. Lilly*, No. 2:15-cv-1202-WCB (June 23, 2016).

The best characterization of Lilly's argument is that somehow it matters that there were some undiscovered PDE5 inhibitors in July 1997. *See* Ex. 4, Rotella WD Decl. ¶ 73 at App. 0121-22 (citing avanafil). But avanafil, and other such later-discovered PDE5 inhibitors do not meaningfully add to the number or breadth of PDE5 inhibitors known in July 1997. Ex. 78, Bell Decl. ¶ 57 at App. 1587. In all events, UroPep did not need to describe every later-invented embodiment, and if these PDE5 inhibitors can be used to treat BPH, their use to do so is covered by the claims, which are fully described because the inventors demonstrated possession of their invention to persons of skill in the art aware of hundreds of PDE5 inhibitors.

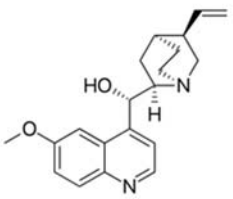
Lilly's position is that even when the "structural diversity" of a class of agents is known in the art, no one can invent a new treatment referring generically to that class of agents for the simple reason that they are structurally diverse. That is not the standard for demonstrating possession of a new therapy, and it reconfirms why the state of the art is such an important consideration in deciding whether a representative number of species has been presented. Looking at other cases and Lilly's own patents, including patents on PDE5 inhibitors, and pausing to consider the implications of Lilly's argument to other classes of drugs shows just how disruptive Lilly's rule would be and how wrong it is.

E. Looking To Other Pharmaceutical Therapy Inventions, Including Lilly's Own, Shows How Disruptive Its Rule Would Be And How Wrong It Is

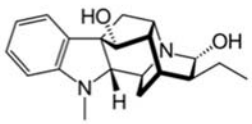
Lilly shrouds itself in the repeated refrain that PDE5 inhibitors are "structurally diverse,"[23] and the unspoken conclusion (when forced to account for *LizardTech* and the knowledge of a person of skill) is that UroPep could have listed every PDE5 inhibitor known in July 1997 and still not adequately described the class. Lilly WD Br. 2, 4, 13, 14, 17. Lilly's position cannot be squared with the nature of pharmaceutical innovation and other pharmaceutical patents, including its own.

Take, as a first example, the patent-in-suit in *Avanir*. As noted earlier, it claimed "a debrisoquin hydroxylase inhibitor," in a combination drug product. Debrisoquin hydroxylase is otherwise known as CYP2D6. Ex. 78, Bell Decl. ¶ 69, App. at 1591. As with PDE5 inhibitors, CYP2D6 inhibitors exhibit widely diverse chemical structures. Ex. 78, Bell Decl. ¶¶ 70-72, App. at 1591-92; Ex. 65, App. at 1362, 1365, U.S. Patent No. RE38,115 (the patent-in-suit in *Avanir*) at col. 4, ll. 33-45 (identifying "quinidine, nortriptyline, chlorpromazine, domperidone, haloperidol, pipamerone, labetalol, metaprolol, oxprenolol, pronanolol, timolol, mexiletine, quinine, diphenhydramine, ajmaline, lobeline, papaverine, and yohimbine.") Just look at the chemical structural diversity of a few of these:

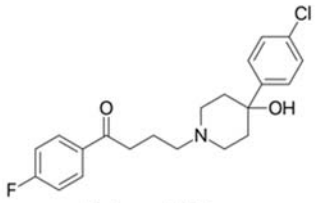
[23] While UroPep agrees that PDE5 inhibitors have diverse *chemical* structures, they share common physical structural features, including the presence of a flat planar region and neighboring hydrogen bond donor/acceptor which enable them to bond to the PDE5 catalytic site. Bell Decl. *Id.* ¶ 50, App. at 1583. The parties also have a factual dispute on this subject, as Lilly's expert has opined that not all PDE5 inhibitors bind to the same region of PDE5. Ex. 4, Rotella WD Decl. ¶ 8.e, App. at 0097. The science, and Dr. Bell, disagree. Ex. 78, Bell Decl. ¶ 50, App. at 1583



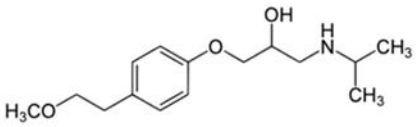
quinidine



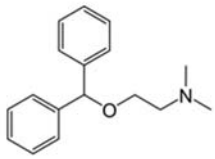
ajmaline



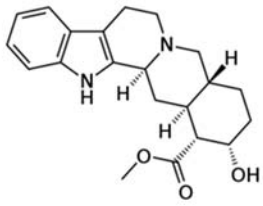
haloperidol



metaprolol



diphenhydramine

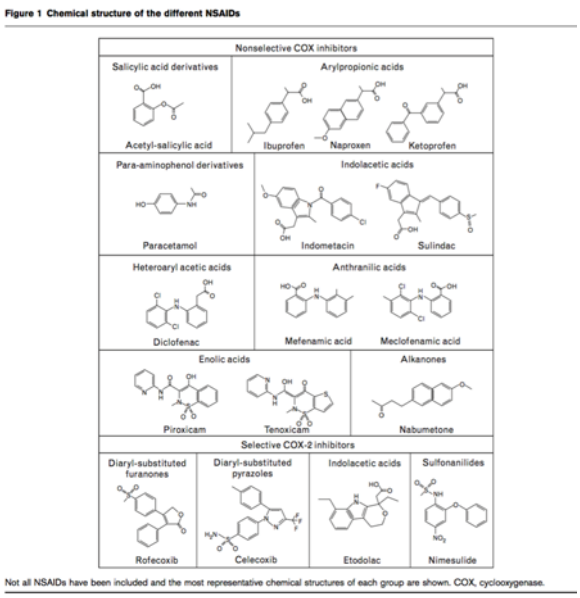


yohimbine

Ex. 78, Bell Decl. ¶ 70, App. at 1591. Those are just some of the CPY2D6 inhibitors mentioned in the patent from *Avanir*, but there are many other CYP2D6 inhibitors not mentioned, with different structures from these. Ex. 78, Bell Decl. ¶ 71, App. at 1591-92; Ex. 66, Mayo Clinic List Of CYP2D6 Inhibitors, App. at 1374.

Lilly's rule means that Avanir's patent is invalid, because no one could claim the use of these inhibitors given their structural diversity and the impossibility of naming every one of them. The fact that a sophisticated ANDA litigant never raised this written description argument — on a patent litigated through judgment — tells us something.[24] It provides at least circumstantial evidence that those who frequently practice in this area do not regard it as a particular problem to claim a class of even structurally diverse but known agents for use in a new method or combination drug product.

[24] *See Avanir Pharm., Inc. v. Actavis S. Atl. LLC,* 36 F. Supp. 3d 475, 509 (D. Del. 2014), *appeal dismissed sub nom. Avanir Pharm. Inc. v. Par Pharm. Inc.,* 574 F. App'x 940 (Fed. Cir. 2014)*, and aff'd sub nom. Avanir Pharm. Inc. v. Par Pharm. Inc.*, 612 F. App'x 613 (Fed. Cir. 2015).



This is far from a one-off. Non-steroidal anti-inflammatory drugs, or NSAIDs, represent a diverse and eclectic group of chemical structures more defined by their shared ability to inhibit the COX enzymes than anything else. Ex. 50, Rotella Dep. at 75:18-24, 77:2-11, App. at 0953-54; Ex. 78, Bell Decl. ¶ 54, App. at 1585-86; Ex. 67, App. at 1377, Canto 2009 (Fig. 1 at left). Yet, the community of inventors frequently claims these structurally diverse but well known agents as a class. The term "NSAID" is in the claims of 569 issued U.S. patents;[25] the term "non-steroidal anti-inflammatory drug" is in the claims of 381.[26] While review of all of these would exceed the page limits allowed for this brief, we can examine one. Lilly's U.S. Patent No. 6,245,802, claims:

> A method for treating pain in a mammal requiring said treatment, which comprises administering to said mammal an effective amount of duloxetine or a pharmaceutically acceptable salt or solvate thereof; in combination *with an effective amount of one or more NSAIDs* or acetaminophen.

Ex. 68, App at 1389, col. 9, ll. 56-60 (emphasis added). Lilly, when it is obtaining patents on a new therapy, feels comfortable claiming a known group of agents as a class, even when they are as structurally diverse as NSAIDs. The specification of Lilly's adequately-described patent even says

[25] http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=0&f=S&l=50&TERM1=NSAID&FIELD1=ACLM&co1=AND&TERM2=&FIELD2=&d=PTXT (last visited August 8, 2016).

[26] http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&u=%2Fnetahtml%2FPTO%2Fsearch-adv.htm&r=0&f=S&l=50&d=PTXT&RS=ACLM%2FNSAID&Refine=Refine+Search&Query=ACLM%2F%22non-steroidal+anti-inflammatory+drug%22 (last visited August 8, 2016).

that it covers yet-to-be-discovered NSAIDs. *Id.* at col. 2, l. 59 - col. 3, l. 15, App. at 1385-86 (defining NSAID as "a non-steroidal anti-inflammatory agent which can be identified as such by the skilled artisan" and noting that "new NSAIDs may be in development, and the present invention contemplates … such new agents … as well.").[27]

We can anticipate that Lilly will tell us that NSAIDs were even more well-known than PDE5 inhibitors or some other fact-based distinction inappropriate for a summary judgment motion. But remember, Lilly has patents on the use of PDE5 inhibitors as a class, of relatively the same vintage as the UroPep patent. Lilly has represented to the USPTO that such claims are patentable, and should not be heard by this Court to object to the same rules it applies to itself being used to validate UroPep's invention. *Cf. Diamond Scientific Co. v. Ambico, Inc.,* 848 F.2d 1220, 1224 (Fed. Cir. 1988) (the doctrine of assignor estoppel prevents a patentee who has assigned for value from later challenging the validity of what he has assigned).

F. Lilly's PDE5 Inhibitor Patents Are Its Concession That Claims Can Be Directed To The Class

As discussed earlier, *see supra* 14, in 1999 Lilly filed for a patent application that led to United States Patent No. 6,451,807 and claims uses of a "selective PDE5 inhibitor" to treat sexual dysfunction in specific patient subpopulations. Ex. 56 at col. 20, ll. 45-56, App. at 1121. That patent contains the following language that is at odds with Lilly's position in this case that no one could lay claim to a new method using PDE5 inhibitors in 1997:

> Selective PDE5 inhibitors vary significantly in chemical structure, and the use of a selective PDE5 inhibitor as defined in the present

[27] Lilly's expert Dr. Rotella provided a list of enzymes that have structurally diverse inhibitors, and the sweeping nature of Lilly's argument would mean that no one could patent a therapy using the classes of these inhibitors. *See* Ex. 50, Rotella Dep. at 78:1-14, App. at 0954 (listing such enzymes as HIV protease, kinase, HIV integrase, serine proteases, and dipeptidyl peptidase). Of course, as just one example Lilly has numerous patents claiming the use of kinase inhibitors as an entire class without specification of any particular structure. *See* Ex. 54, entries 6, 10, 13, 14, 15, 16, 17, 18, and 22, App. at 1096-98.

> invention is not dependent on a particular chemical structure, but rather on the critical parameters outlined herein.

Id. col. 7, ll. 3-7, App. at 1115.

Another Lilly patent is even broader. U.S. Patent No. 6,492,371 bears a priority date of April 2000,[28] and claims

> A method of treating Parkinson's Disease comprising administering a therapeutically effective amount of a compound that inhibits cGMP-specific phosphodiesterase (PDE5).

This language is nearly identical to what appears in the '124 patent claims. And here again, Lilly obtained a patent that says "PDE5 inhibitors useful in the present invention vary significantly in chemical structure and the use of a PDE5 inhibitor in the present method is not dependent on a particular chemical structure." *Id.* at col. 4, ll. 38-41, App. at 1393. Neither of these Lilly patents come anywhere close to specifying all the different structural motifs of PDE5 inhibitors. Ex. 78, Bell Decl. ¶¶ 66-67, App. at 1590. Claiming new uses of the known and structurally diverse class of PDE5 inhibitors was not a problem for Lilly until it was potentially liable for infringement of the '124 patent.

The '124 patent provides more than enough representative examples for use in its new therapeutic method. Summary judgment must be denied because this is a new use of a known class of compounds — where a person of skill would be aware of hundreds of such compounds — not an alleged invention of a broad genus of compounds with the provision of an unrepresentative set. The presentation of several example PDE5 inhibitors in the '124 patent[29] is more than enough to

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[28] Ex. 69, '371 patent, col. 12, ll. 26-29, App. at 1397. This patent was assigned to Lilly even before it issued in December 2002, because its parent application was so assigned. *See* http://assignment.uspto.gov/#/assignment?id=11915-292&q=patAssignorName%3A(Roylance) (last visited August 8, 2016).

[29] At times Lilly suggests that the '124 patent fails to disclose that its examples are PDE5 inhibitors. *See* Lilly 112 ¶ 6 Br. 6. Lilly's expert put that issue away, conceding that nearly all of the examples were known as PDE5 inhibitors. Ex. 50, Rotella Dep. at 67:4-12, App. at 0951. Dr. Rotella said he

demonstrate possession of a therapeutic method, and the parties have a fact dispute regarding the state of the art in 1997 (on which UroPep is presumed to be, and is, correct).

For all of Lilly's extended discussion of "structural diversity," these compounds work in the same way, in pursuit of the identical function to achieve the same result because they share physical structural characteristics. Even in the event that the Court applies § 112 ¶ 6, summary judgment of non-infringement should also be denied.

III. EVEN IF § 112 ¶ 6 APPLIES, THE USE OF CIALIS IN THE PATENTED METHOD INFRINGES BECAUSE TADALAFIL IS AN EQUIVALENT TO THE DISCLOSED PDE5 INHIBITORS

The claim term "an inhibitor of phosphodiesterase (PDE) V" is not a means plus function term, because *Epcon Gas* bars such an interpretation and because the word "inhibitor" conveys a compound and thus structure. But even indulging in Lilly's assumption about the claim construction, the use of Cialis to treat BPH still infringes the UroPep claims because tadalafil is an equivalent to identified structures in the '124 patent specification.

Lilly's analysis begins on the wrong foot, assuming that the elimination of specific named compounds from the scope of the asserted claims (the so-called "negative Markush group") by silent implication eliminated the equivalents to those molecules. This is wrong as a matter of claim construction, and neither of the two cases Lilly cites support the conclusion that prosecution history disclaimer applies to this situation. The case law on claim differentiation shows that positive selection of a specific structure in a claim that depends on a means plus function claim includes only that structure and not its equivalents. Likewise, elimination of a specific structure eliminates only that structure and not its equivalents. Moreover, there is no evidence whatsoever that the inventors

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could not find example (j) of the '124 patent in the literature even though he looked for it. *Id.* at 66:4-9, 67:14-18. It was in one of Dr. Rotella's own exhibits, disclosed as a PDE5 inhibitor. Ex. 26, Takase 1993, at 1766, App. at 0451; Ex. 78, Bell Decl. ¶ 36, App. at 1575.

intended to disclaim equivalents to the negative Markush compounds, much less "clear and unambiguous" disavowal of claim scope.

Lilly's zeal to eliminate equivalents of the negative Markush group becomes apparent when one looks to whether tadalafil has the identical function (PDE5 inhibition), performs that function in substantially the same way (binding to the catalytic site of the PDE5 enzyme), and achieves substantially the same result in performing its function (has similar potency) to at least two of the structures identified in the '124 patent. Specifically, tadalafil is an equivalent to sildenafil, as well as compound (d) of the '124 patent, the latter of which contains the 3,4-methylenedioxyphenyl moiety that is critical to tadalafil's binding in the catalytic site of PDE5.

At a minimum, these disputed fact issues preclude summary judgment of non-infringement.

A. The Negative Markush Group Does Not Silently Subtract Equivalents Of Those Compounds

The negative Markush group does just what it says, it removes the eight listed structures from the scope of the claim, no more and no less. Lilly invokes prosecution history estoppel, but there has been no clear and unambiguous disavowal, which is what the case law requires. And the case law on interpreting dependent claims in means plus function patents shows how positive and negative selections should be read — the negative Markush group leaves behind all structural equivalents.

1. There has been no clear and unambiguous disavowal of claim scope

In order for prosecution history estoppel to apply "the statement in the prosecution history must be clear and unambiguous, and constitute a clear disavowal of scope." *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1306 (Fed. Cir. 2007). Lilly points to the introduction of the negative Markush group in the prosecution to obviate a double patenting rejection. Lilly 112 ¶ 6 Br. 20. But the relevant amendment nowhere addresses the equivalents to the excised compounds, and

nowhere shows an intent to resect more than what was stated. Ex. 49, '124 at 217-221, App. at 0910-0914. In fact, equivalents to the removed compounds are never discussed at all. *Id.*

From the observation that sometimes prosecution history estoppel can apply in a means plus function case, Lilly 112 ¶ 6 Br. 20-21, Lilly leaps to the conclusion that any express exclusion of a specific structure always carries with it all of its equivalents. But the cases Lilly relies on in no way support that proposition. In *Regents of Univ. of Minnesota v. AGA Med. Corp.*, 717 F.3d 929, 943 (Fed. Cir. 2013), the court held that a clear and unambiguous disclaimer of claim scope in a parent prosecution of claims not subject to § 112 ¶ 6 did not carry forward to claims in a subsequent application that were deemed to contain means plus function limitations. In the course of so determining, the court observed that the doctrine of prosecution history estoppel applies to means plus function claims, *id.* at 942, and then found it did not apply to the claims at issue. *Id.* at 943. And in *Alpex Computer Corp. v. Nintendo Co.*, 102 F.3d 1214, 1221 (Fed. Cir. 1996), "during the prosecution of the [patent-in-suit], Alpex described the means-plus-function limitation under § 112, ¶ 6, as not covering a shift register-based video display system." In other words, there the applicant specifically disclaimed the alleged equivalent. In this case the corollary would be if the inventors told the USPTO "we are not attempting to cover tadalafil." That did not happen.

Lilly's authorities do not establish its proposition that a negative claim limitation like this one always carries out with the named elements all equivalent structures. Examination of the authorities on claim differentiation with respect to means plus function claims indicate the opposite.

2. The authorities dealing with claim differentiation with respect to means plus function claims support the interpretation that the negative Markush group did not remove structural equivalents to the removed compounds

In *Pressure Products Medical Supplies, Inc. v. Greatbatch Ltd.*, 599 F.3d 1308, 1317 (Fed. Cir. 2010), the base independent claim of the patent in suit required a "means for permitting removal." *Id.*

Dependent claims required that the means of claim 1 be "a score line." *Id.* The patentee argued under the doctrine of claim differentiation that the base claim must include structures other than score lines and the court rejected this argument, ruling that the positive recitation of a specific structure did not include its structural equivalents:

> This argument fails, however, because a means-plus-function claim element already includes structures other than the corresponding structure explicitly described in the specification, namely, equivalents of the corresponding structure. *See* 35 U.S.C. § 112, ¶ 6. Therefore, as the means-plus-function claim element of claim 1 includes the equivalents of score lines, the magistrate judge's claim construction does not violate the doctrine of claim differentiation.

Id. at 1317-18; *accord Medtronic, Inc. v. Advanced Cardiovascular Sys., Inc.*, 248 F.3d 1303, 1313 (Fed. Cir. 2001) ("It is settled law, however, that independent claims containing means-plus-function limitations do not have the same literal scope as dependent claims reciting specifically the structure that performs the stated function."); *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991) (same). The law is that specific recitation of structure refers only to that structure and not its equivalents. The application of that principle here means that the specific recitation of structure in the negative Markush group removed only those structures and not their equivalents.

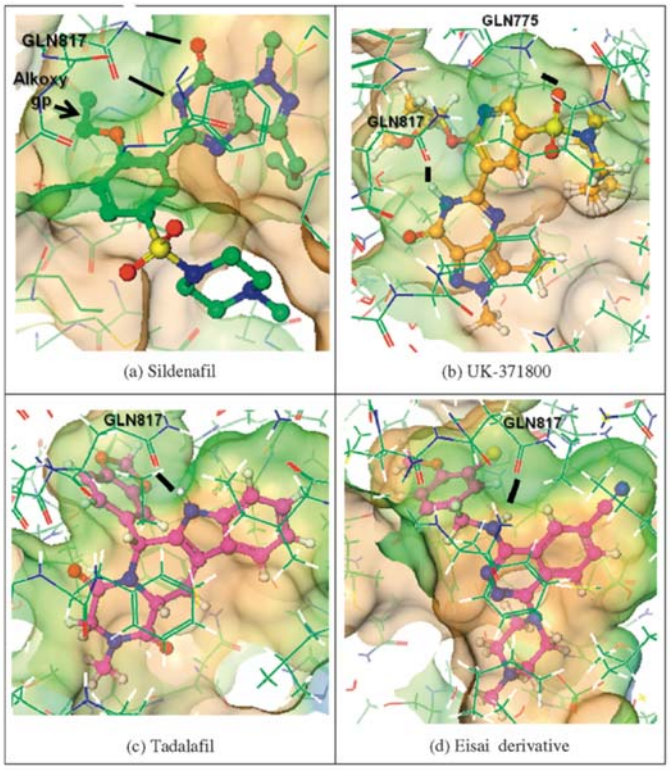
Lilly needed to get rid of sildenafil and compound (d) because they are equivalents to tadalafil with respect to what matters — they bind to the catalytic site of PDE5 in substantially the same way and they are equally potent as PDE5 inhibitors and thus achieve substantially the same result. Lilly infringes even if the claim term is subject to § 112 ¶ 6.

B. Lilly Infringes Even If § 112 ¶ 6 Applies Because Tadalafil Is Equivalent To Sildenafil And Compound (d) Of The '124 Patent

Lilly does not contest that all the disclosed compounds in the '124 patent perform an identical function — PDE5 inhibition. Instead Lilly focuses its distinctions on the way and result prongs of equivalency. Lilly 112 ¶ 6 Br. 24-29. Lilly seizes on every difference tadalafil has with the

two non-excluded structures, zaprinast and MY5445 (focusing in the wrong place for reasons described above), but engages in no analysis as to what the "way" and "result" part of equivalents means here, in this patent, which covers the treatment of BPH through administration of an effective amount of a PDE5 inhibitor.

For an equivalency analysis the "way" is how the alleged equivalent performs its function. *Odetics, Inc. v. Storage Tech. Corp.*, 185 F.3d 1259, 1267 (Fed. Cir. 1999). In this context that refers to where on the PDE5 enzyme the inhibitor binds (because that is what inhibitors do). Ex. 78, Bell Decl. ¶ 87, App. at 1595. Lilly's argument on the "way" prong reduces to the observation that all inhibitors bind differently. That is an irrelevant truism in that every pair of distinct inhibitors will bind slightly differently to the same enzyme. Ex. 78, Bell Decl. ¶ 89, App. at 1596. The question is whether the accused equivalent, here tadalafil, binds in substantially the same way as the structures of the '124 patent. The answer is yes. First, all known PDE5 inhibitors bind to the same site on the PDE5 enzyme (albeit in slightly different orientations that are not substantially different). Ex. 78, Bell Decl. ¶¶ 87, 89, App at 1595-96 (citing Ex. 71, App. at 1420, S.H. Francis, et al., *Inhibition of Cyclic Nucleotide Phosphodiesterases by Methylxanthines and Related Compounds* in B.B. Fredholm (ed.), *Methylxanthines*, Handbook of Experimental Pharmacology 200 (2011)). Second, it can easily be seen from reported crystal structures that tadalafil and sildenafil, as well as compounds related to structure (d), bind to PDE5 in



substantially the same way. Ex. 70, App. at 1404-05, A.S. Bell, *The Discovery of the Long-acting PDE5 Inhibitor PF-489791 for the Treatment of Pulmonary Hypertension* at 169 ("Bell 2011") (previous page). In the illustrated structures, each PDE5 inhibitor is shown in the same binding pocket, the catalytic site of PDE5. Ex. 78, Bell Decl. ¶ 89, App. at 1596. As can be seen, all four PDE5's make a hydrogen bond linkage to the glutamine of PDE5. And as is also seen, the binding of the 3,4-methylenedioxyphenyl moiety of tadalafil (upper left of its diagram) is very similar to the binding of the Eisai compound that is structurally related to compound (d) of the '124 patent. Ex. 78, Bell Decl. ¶ 89, App. at 1596. In short, yes they all bind slightly differently, but they all bind in substantially the same way. There is, at the least, a fact issue.

On the "result" prong, Lilly's approach is the kitchen sink of differences between tadalafil and the structures of the '124 patent. Again, Lilly never asks what the result is in the context of the function that it has identified — PDE5 inhibition. To use an analogy, if the functional claim term is "means for driving a nail through a piece of wood," and the associated structure a hammer, the function is driving a nail through a piece of wood, the way is by striking the nail with force in parallel to the nail, and the result is how well the nail is driven through the wood. The result is not whether the hammerer gains upper body strength or whether the head of the nail is scratched or not, because those results are unrelated to the function.

In this case the function is PDE5 inhibition, and the result is the effect (and effectiveness) of using the structures and their equivalents for PDE5 inhibition — *i.e.* potency. Ex. 78, Bell Decl. ¶¶ 86, 90-91, App. at 1595-97. To its credit, this is the first result Lilly discusses. Lilly 112 ¶ 6 Br. 26. But then Lilly takes a detour into body-building and nail-scratching by discussing selectivity and

pharmacokinetics.[30] In all events, sildenafil and compound (d) have substantially the same potency for PDE5 inhibition as tadalafil, and therefore tadalafil is an equivalent, and infringing, structure. Ex. 78, Bell Decl. ¶ 91, App. at 1597. Further, sildenafil has substantially the same selectivity. Ex. 78, Bell Decl. ¶ 92, App. at 1597. That leaves just pharmacokinetics, which might be relevant if the claims of the '124 patent recited a particular dosage regimen for the method, but they do not, and thus pharmacokinetics is not relevant. Ex. 78, Bell Decl. ¶ 63, App. at 1589.

Tadalafil is an equivalent structure to those disclosed in the '124 patent and thus, even if the Court applies § 112 ¶ 6 to UroPep's asserted claims, there is a fact issue as to infringement that precludes summary judgment.

CONCLUSION

For the foregoing reasons, Lilly's motions for summary judgment should be denied.

[30] Lilly's expert conceded that the relevant result is the inhibition of PDE5. Ex. 50, Rotella Dep. at 81:13-22, App. at 0955 ("[t]he functional result is that tadalafil and MY5445 and zaprinast initiate [sic] PDE5. That functional result is similar.").

RESPONSE TO LILLY'S STATEMENT OF UNDISPUTED FACTS

UroPep provides the following responses to Lilly's statements of undisputed facts in its motions, in corresponding numbered paragraphs.

Written Description

1. Undisputed.

2. UroPep disputes that this is a proper construction of "compound." To the extent that Lilly is attempting to capture later-invented species like the 2013-publication of a PDE5 antibody, UroPep disputes that this is within the scope of the claim term. *See*, *supra*, at 31-32.

3. UroPep disputes that the "field of PDE inhibitors was emerging and unpredictable." Lilly bases this assertion on a misreading of Dr. Terrett's 1996 article and a selective quotation from it. The article does not say that *in 1996* "very little had been reported on the design, synthesis and screening of selective cGMP PDE inhibitors," it says "*Prior to our work*, very little had been reported …." Ex. 12, Terrett 1996, App. at 0318 (emphasis added). In reality, and as a person of skill would know, Dr. Terrett's work began in 1985, with a first patent publication in 1991 from a 1990 priority application. *See, supra* at 25; Ex. 78, Bell Decl. ¶¶ 19-31, App. at 1571-73.

4. UroPep disputes that significant additional structural diversity has been added to the field of PDE5 inhibitors since July 1997. Ex. 78, Bell Decl. ¶ 57, App. at 1587.

5. UroPep does not dispute this statement, insofar as it is understood to be referring to chemical structural similarity and not physical or topological structural similarity, which all PDE5 inhibitors share. Ex. 78, Bell Decl. ¶ 50, App. at 1583.

6. UroPep does not dispute that all classes of drugs exhibit variation in these characteristics within the class.

7. UroPep disputes that the '124 patent discloses compounds as potential candidates for PDE5 inhibitors. It discloses compounds that the person of skill in the art would know are PDE5 inhibitors. Ex. 78, Bell Decl. ¶¶ 39, 45-46, App. at 1580-82.

8. UroPep agrees that the '124 patent does not say that the disclosed compounds are PDE5 inhibitors, but disputes the relevance of this fact, given that a person of skill in the art would know that they were PDE5 inhibitors. Ex. 50, Rotella Dep. at 67:4-12, App. at 0951; Ex. 78, Bell Decl. ¶ 64, App. at 1589-90.

9. Undisputed.

10. Undisputed.

11. UroPep disputes this claim construction, given that the claim term in dispute covers "compound[s] able to inhibit phosphodiesterase (PDE) V."

12. Undisputed.

13. UroPep disputes the relevance of this fact but agrees that the classes cover theoretically many compounds.

14. UroPep disputes the relevance of this fact given that the '124 patent identifies how to determine whether any particular compound is, in fact, a PDE5 inhibitor. Ex. 1, '124 patent at col. 7, l.18 - col. 8, l. 16, App. at 0006; Ex. 6, Terrett Decl. ¶¶ 36-49, App. at 0184-87. As the '124 patent provides examples of the subject classes, *see supra* at 40, n. 29, it is not true that "the '124 patent does not state which compounds within the classes … would inhibit PDE5."

15. UroPep disputes this fact insofar as it implies that the person of skill in the art would need to know such a relationship in order to understand that the '124 patent inventors were, in fact, in possession of the claimed invention.

16. Undisputed.

17. UroPep disputes this fact given that all PDE5 inhibitors bind to the same catalytic site on the PDE5 enzyme. *See supra* at 41-45; Ex. 78, Bell Decl. ¶ 50, App. at 1583.

18. UroPep does not dispute this fact, except insofar as it is presented as an example of the theory of ¶ 17.

19. UroPep disputes this fact given that all PDE5 inhibitors bind to the same catalytic site on the PDE5 enzyme. *See supra* at 41-45; Ex. 78, Bell Decl. ¶ 50, App. at 1583.

20. UroPep disputes this fact and its relevance, as Lilly has admitted that the tricyclic and tetracyclic PDE5 inhibitors were known to a person of skill and the test for written description takes into account the knowledge of a person of skill in the art.

21. UroPep does not dispute this fact but does dispute its relevance given Lilly and its expert's admissions regarding the widespread knowledge of these structures in the art.

22. UroPep does not dispute this fact but does dispute its relevance given Lilly and its expert's admissions regarding the widespread knowledge of these structures in the art.

23. Undisputed

24. UroPep disputes that the '124 inventors had to describe tadalafil, which Lilly and its expert admits was known in the art prior to July 1997. *See* Ex. 4, Rotella WD Decl. ¶ 64, App. at 0119; Lilly 112 ¶ 6 Br. 29

25. UroPep agrees that tadalafil is not named in the '124 patent.

26. UroPep does not agree that it contends tadalafil infringes claims 1 and 3 of the '124 patent. The use of tadalafil to treat BPH infringes claims 1 and 3.

27. UroPep disputes that this was known to a person of skill in the art as of July 1997, as Lilly has not presented any facts to support this supposition. UroPep agrees that icariin is today known as a PDE5 inhibitor.

28. UroPep agrees that icariin is not named in the '124 patent.

29. UroPep disputes this fact and it is not supported by the cited portions of the declaration of Lilly's expert.

Non-Infringement

1. UroPep does not dispute that the '124 Patent discloses "[p]referred selective inhibitors of PDE I, PDE IV and PDEV." Ex. 1, '124 Patent, col. 2, l. 28, App. at 0003.

2. UroPep agrees that the '124 patent does not say that the disclosed compounds or classes of compounds are PDE5 inhibitors, but disputes the relevance of this fact, given that a person of skill in the art would know that they were PDE5 inhibitors. Ex. 50, Rotella Dep. at 67:4-12, App. at 0951; Ex. 78, Bell Decl. ¶¶ 39, 45-46, App. at 1580-82.

3. UroPep does not dispute that the specification includes the quoted language.

4. UroPep does not dispute that ten "[p]referred selective inhibitors of PDE I, IV and V" are identified by chemical name and/or structure in the specification, and are labelled "a" through "j." Ex. 1, '124 Patent, col. 2, l. 28- col. 4, l. 44, App. at 0003-04.

5. Undisputed.

6. Undisputed.

7. Undisputed.

8. UroPep disagrees that compound "j" in the specification is in the class of pyrazolopyrimidones, and that contention is not supported by the cited portions of the declaration of Lilly's expert.

9. UroPep disagrees, because compound "i" in the specification is in the class of pyrazolopyrimidones. UroPep does not dispute the remaining facts in this paragraph, but does dispute the relevance of these facts, given Lilly and its expert's admissions regarding the widespread knowledge of PDE5 inhibitors in the art. Ex. 50, Rotella Dep. 44:16-21, App at 0945, Ex. 78, Bell Decl. ¶¶ 39, 45-48, App. at 1580-82.

10. UroPep disputes that the number of compounds that fall within the classes of quinazolines and their trimethoxy derivatives or pyrazolopyrimidones is unknowable, and that contention is not supported by the cited portions of the declaration of Lilly's expert. UroPep does not dispute that these classes cover theoretically many compounds, but disputes the relevance of that fact.

11. UroPep does not dispute that Dr. Terrett testified that the class of quinazolines could conceivably include billions of compounds, but disputes the relevance of that fact.

12. UroPep does not dispute that some compounds within the classes of quinazolines and their trimethoxy derivatives or pyrazolopyrimidones may not inhibit PDE5, but disputes the relevance of that fact as the '124 patent identifies how to determine whether any particular compound is, in fact, a PDE5 inhibitor. Ex. 1, '124 patent at col. 7, l.18 - col. 8, l. 16, App. at 0006; Ex. 6, Terrett Decl. ¶¶ 36-49, App. at 0184-86.

13. UroPep does not dispute that the '124 patent does not disclose example compounds within the classes of quinazolines and their trimethoxy derivatives or pyrazolopyrimidones other than compounds d, e, g, and i. UroPep disputes the relevance of this fact, as the exclusion of those example compounds does not also exclude equivalents of those compounds. UroPep does not dispute that the '124 patent does not describe the structure of compounds in those classes, but UroPep disputes the relevance of this fact, as the structures of these classes are known, including to Lilly's expert. Ex. 4, Rotella WD Decl. ¶61, App. at 0117-18.

14. UroPep disputes this as an erroneous claim construction. Even assuming applicability of § 112 ¶ 6, the equivalents of the negative Markush group have not been excluded from coverage of the claim for the reasons stated in UroPep's brief.

15. Undisputed.

16. Undisputed.

17. Undisputed.

18. Undisputed.

19. Undisputed.

20. Undisputed.

21. Undisputed.

22. UroPep disputes that the '124 inventors had to describe tadalafil, which Lilly and its expert admits was known in the art prior to July 1997. See Ex. 3, Rotella Decl. ¶ 64; Lilly 112 ¶ 6 Br. 29, Ex. 50, Rotella Dep. at 35:1-18, App. at 943.

23. UroPep disputes this fact given that all PDE5 inhibitors bind to the same catalytic site on the PDE5 enzyme and because tadalafil is an equivalent to sildenafil, as well as compound (d) of the '124 patent, the latter of which contains the 3,4-methylenedioxyphenyl moiety that is critical to tadalafil's binding in the catalytic site of PDE5. See *supra* at 41-45; Ex. 78, Bell Decl. ¶¶ 61-62, App. at 1588-89. In addition, sildenafil and compound (d) have substantially the same potency for PDE5 inhibition as tadalafil. Ex. 78, Bell Decl. ¶¶ 90-91, App. at 1596-97. Further, sildenafil has substantially the same selectivity. Ex. 78, Bell Decl. ¶ 92, App. at 1597.

24. UroPep disputes the relevance of these facts because tadalafil is an equivalent to sildenafil, as well as compound (d) of the '124 patent, the latter of which contains the 3,4-methylenedioxyphenyl moiety that is critical to tadalafil's binding in the catalytic site of PDE5. In addition, sildenafil and compound (d) have substantially the same potency for PDE5 inhibition as tadalafil. Ex. 78, Bell Decl. ¶¶ 90-91, App. at 1596-97. Further, sildenafil has substantially the same selectivity. Ex. 78, Bell Decl. ¶ 92, App. at 1597. UroPep also disputes the relevance of these facts given Lilly and its expert's admissions regarding the widespread knowledge of tricyclic and tetracyclic PDE5 inhibitors in 1997, including tadalafil. See *supra* at 24, *id.* at n.17; Ex. 78, Bell Decl. ¶¶ 39, 45-48, App. at 1580-82.

25. Undisputed.

26. Undisputed.

27. UroPep does not dispute this fact but does dispute its relevance given Lilly and its expert's admissions regarding the widespread knowledge of tricyclic and tetracyclic PDE5 inhibitors in 1997. See *supra* at 24, *id.* at n.17.

28. Undisputed.

29. Undisputed.

30. UroPep disputes this fact, given that all PDE5 inhibitors bind to the same site on the PDE5 enzyme (albeit in slightly different orientations that are not substantially different). Ex. 78, Bell Decl. ¶¶ 87, 89, App. at 1595-96 (citing Ex. 71, App. at 1420).

31. Relevance disputed for the reasons stated in ¶ 30.

32. Undisputed.

33. UroPep disputes these facts. All PDE5 inhibitors bind to the same site on the PDE5 enzyme (albeit in slightly different orientations that are not substantially different). Ex. 78, Bell Decl. ¶¶ 87, 89, App. at 1595-96 (citing Ex. 71, App. at 1420). Tadalafil and sildenafil, as well as compounds related to structures (d) and (f), bind to PDE5 in substantially the same way. In illustrated structures, each of these PDE5 inhibitor is shown in the same binding pocket, the catalytic site of PDE5. Ex. 78, Bell Decl. ¶¶ 87, 89, App. at 1595-96. All four PDE5's make a hydrogen bond linkage to the glutamine of PDE5. And as is also seen, the binding of the 3,4-methylenedioxyphenyl moiety of tadalafil (upper left of its diagram) is very similar to the binding of the Eisai compound that is structurally related to compounds (d) and (f) of the '124 patent. Ex. 78, Bell Decl. ¶¶ 61-62, 87-89; App at 1588-89, 1595-96.

34. Disputed for the reasons stated in ¶ 33.

35. Disputed for the reasons stated in ¶ 33.

36. Undisputed.

37. Undisputed.

38. UroPep disputes the relevance of this fact, given that tadalafil has substantially the same potency as sildenafil and compound (d), and substantially the same selectivity as sildenafil. See Ex. 78, Bell Decl., ¶¶ 90-92, App. at 1596-97.

39. UroPep does not dispute that the table here shows data on potency of tadalafil and zaprinast. UroPep notes that this table also shows the potency of sildenafil which, as shown here, is identical to the potency for tadalafil. This table also shows how tadalafil is less selective for PDE11 than sildenafil similar to how sildenafil is less selective than tadalafil for PDE6, contributing to the conclusion that tadalafil and sildenafil have similar overall selectivity for PDE5. Ex. 78, Bell Decl. ¶¶ 90-92, App. at 1596-97.

40. UroPep disputes the relevance of this fact for the reasons stated in ¶ 38.

41. UroPep disputes these facts, given that tadalafil has substantially the same potency as sildenafil and compound (d), and substantially the same overall selectivity as sildenafil. Ex. 78, Bell Decl., ¶¶ 90-92, App. at 1596-97.

42. UroPep disputes that sildenafil's selectivity to PDE6 necessarily causes visual disturbances, and disputes that tadalafil and sildenafil have very different selectivity when PDE11 is taken into account, as it should be. Ex. 78, Bell Decl., ¶ 92, App. at 1597.

43. UroPep disputes the relevance of these facts for the reasons stated in ¶ 38.

44. UroPep disputes the relevance of these facts for the reasons stated in ¶ 38.

45. UroPep disputes the relevance of these facts for the reasons stated in ¶ 38.

46. Disputed for the reasons stated in ¶ 23.

47. UroPep disputes the relevance of pharmacokinetic data to any issue in connection with these motions. The claims of the '124 patent do not require any particular dosage or regimen, to which pharmacokinetics is relevant.

48. UroPep disputes the relevance of pharmacokinetic data to any issue in connection with these motions. The claims of the '124 patent do not require any particular dosage or regimen, to which pharmacokinetics is relevant.

49. UroPep disputes the relevance of pharmacokinetic data to any issue in connection with these motions. The claims of the '124 patent do not require any particular dosage or regimen, to which pharmacokinetics is relevant.

50. Undisputed.

51. UroPep disputes the relevance of pharmacokinetic data to any issue in connection with these motions. The claims of the '124 patent do not require any particular dosage or regimen, to which pharmacokinetics is relevant.

Date: August 8, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing document was filed electronically in compliance with Local Rule CV-5(a) on August 8, 2016. As such, this document was served on all counsel who are deemed to have consented to electronic service. Local Rule CV-5(a)(3)(A).

Date: August 8, 2016

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